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April 29, 2019

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Center for Clinical Standards and Quality
Centers for Medicare & Medicaid Services
Mail Stop C3-02-01
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VIA ELECTRONIC DELIVERY TO NCDRequest@cms.hhs.gov

Re: Formal Request for Reconsideration of Artificial Heart National Coverage Determination

Dear Ms. Syrek Jensen:

As a follow up to our meeting on coverage of artificial hearts on June 26, 2018, SynCardia Systems, LLC (SynCardia) is pleased to submit this letter formally requesting reconsideration of the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) on artificial hearts[1] to authorize coverage of the 70cc artificial heart for use as a bridge to transplantation. In light of the additional clinical evidence discussed herein, we believe that the evidence demonstrates that this use is reasonable and necessary under section 1862(a)(1)(A) of the Social Security Act (SSA), and thus coverage with evidence development (CED) for this indication is no longer warranted.

As you know, SynCardia has developed and manufactures a biventricular replacement device that has been marketed as the SynCardia temporary Total Artificial Heart (TAH-t). On May 1, 2008, CMS issued an NCD authorizing coverage for artificial hearts as a bridge to transplantation and as destination therapy via CED.[2] Under the NCD, coverage is contingent on a patient's enrollment in a CMS approved clinical study. There have been a number of clinical studies involving the TAH-t approved by CMS and that have facilitated the development of new evidence not considered for the 2008 NCD that supports full coverage of the 70cc TAH-t as a bridge to transplant. In particular, a study published in the Journal of Heart and Lung Transplantation which considered the data for all adult patients over 19 years of age receiving the TAH-t for whom data were entered in the Intermacs Registry over an 11 year period

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1 NCD 20.9 (National Coverage Determination for Artificial Hearts and Related Devices), available at https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=246&ncdver=6&bc=AAAAgAAAAAAA&. As you know, in this NCD and the related final coverage decision memorandum, CMS identified the pertinent benefit categories as (1) prosthetic devices and (2) inpatient hospital services. We agree that these remain the pertinent categories.

2 *Id.*

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demonstrates the clinical benefits of the SynCardia TAH-t.[3] This represents 79% of the total US population implanted with the 70cc TAH-t during the same period. As reported, at one year, 66% of patients facing certain death who received the TAH-t were alive – most of whom had received a heart transplant by then, but some of whom remained on the TAH-t. Thus, the TAH-t is an FDA-approved durable treatment option for patients with biventricular failure that prolongs the life expectancy for otherwise terminal patients. For these reasons, as amplified below, CMS should reconsider the artificial heart NCD and establish coverage under SSA § 1862(a)(1)(A) for the 70cc TAH-t when used as a bridge to transplant.

INTRODUCTION

According to the American College of Cardiology (ACC) and the American Heart Association (AHA), "heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood."[4] Heart Failure (HF) is progressive and is a common, prevalent and increasing cardiac malady in the United States. Congestive Heart Failure (CHF), as manifested by fluid build-up in the arms, legs, ankles, feet, lungs or other organs, is regarded as the "final common pathway" of all forms of heart disease, as it is the ultimate manifestation of dysfunction, regardless of the initiating cardiac disease. Many patients may need a TAH-t because of biventricular issues from etiologies as varied as acute myocardial infarction, cardiogenic shock, cardiac tumors, arrhythmias, congenital conditions and others (see attached list of etiologies at **Tab 2**). CHF is primarily a disease of older individuals, with the incidence rising progressively with age, affecting 6-10% of the population for those older than 65 years old.[5] Many recipients of the TAH-t also are Medicare beneficiaries because they are disabled.

The natural history of HF is that of disease progression. Over time, patients progress through a series of stages of increasing symptoms, with progressive shortness of breath, reduction in exercise capacity and body and organ edema and congestion. As patients deteriorate, medical therapy fails and the only effective therapy is that of physical replacement of the diseased heart. Some patients require TAH-t intervention even before experiencing CHF. Cardiac transplantation has emerged as the definitive therapy for patients with advanced or end-stage heart failure. Transplantation has demonstrated a one-year survival rate of around 90.5%. The five-year survival rate is approximately 77.7%.[6] Over the past few decades, cardiac transplantation has progressed from being a therapy restricted to younger patients to now being utilized increasingly in older patients. In 2006, the International Society for Heart and Lung Transplant issued updated guidelines on patient selection for heart transplantation which

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3 Arabia, F. et al., *Interagency registry for mechanically assisted circulatory support report on the total artificial heart*, 37 J. Heart & Lung Transplantation 1304 (Nov. 2018) (hereinafter "Arabia-Intermacs Study"). A copy of this study is attached as **Tab 1**.

4 Yancy, CW, *2013 ACCF/AHA Guideline for the Management of Heart Failure,* e153 Journal of the American College of Cardiology, Vol. 62, No. 16, 2013

5 Emory Healthcare Health Connection, Heart & Vascular: Conditions & Treatments, Heart Failure Statistics (https://www.emoryhealthcare.org/heart-vascular/wellness/heart-failure-statistics.html) (last visited 4/25/19).

6 National Post-Transplant Survival Data, cardiac transplants 2008-2015, UNOS (https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#) (last queried April 2019).

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included consideration of adults into their seventies.[7] Since then, the frequency of transplantation in older adults has increased. For example, in 2013 almost 40% of heart transplants occurred in recipients aged 60 and older with over 4% of heart transplants occurring in recipients age 70 and older.[8]

While heart transplantation has been shown to be an effective treatment in the elderly patient population, a significant limitation of cardiac transplantation affecting all ages relates to donor organ availability. Many patients die waiting for a donor heart because of lack of organ availability at the time of decompensation.[9] For 2017, UNOS reports that 7% of patients died while waiting for a donor heart and 8% were removed from the active transplant list because of worsening condition.[10] Not only could the TAH-t serve many of these patients, but there are also patients who are too sick to be on the transplant list for whom the TAH-t could offer a bridge to transplant-eligibility (those patients would not be reflected in the UNOS data).

It is exactly for this problem that the field of durable mechanical circulatory support (MCS) emerged. MCS devices are placed to "bridge" failing patients to transplantation. The only other devices that were available as a bridge were ventricular assist devices (VADs), which may be used singly or dually (biventricular VADs, or BiVADs), to support one or both ventricles. The only FDA-approved pulsatile BiVADs were discontinued in 2016 and are no longer available as a therapy. While some hospitals continue to use dual continuous flow left ventricular assist devices (LVADs) as BiVADs (an off-label use of an approved device), there are currently no other durable FDA-approved devices for biventricular failure in the adult population. Interagency Registry for Mechanically Assisted Circulatory Support (Intermacs) data, comparing the continuous flow BiVAD configuration currently in use with the TAH, shows a death rate of 49% for BiVADs, while the TAH death rate is 35%.[11]

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7 Cooper, L., *Cardiac Transplantation for Older Patients: Characteristics and Outcomes in the Septuagenarian Population,* 35 J. Heart & Lung Transplantation 362 (2016).

8 *Id.* at 366-68.

9 Copeland, J, et al., *Cardiac Replacement with a Total Artificial Heart as a Bridge to Transplantation,* 351 N. Engl. J. Med 859, 860 (2004).

10 National Post-Transplant Survival Data, UNOS (https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#) (last queried April 2019).

11 Intermacs Quarterly Statistical Report, Q1 2017, Exhibit 13.

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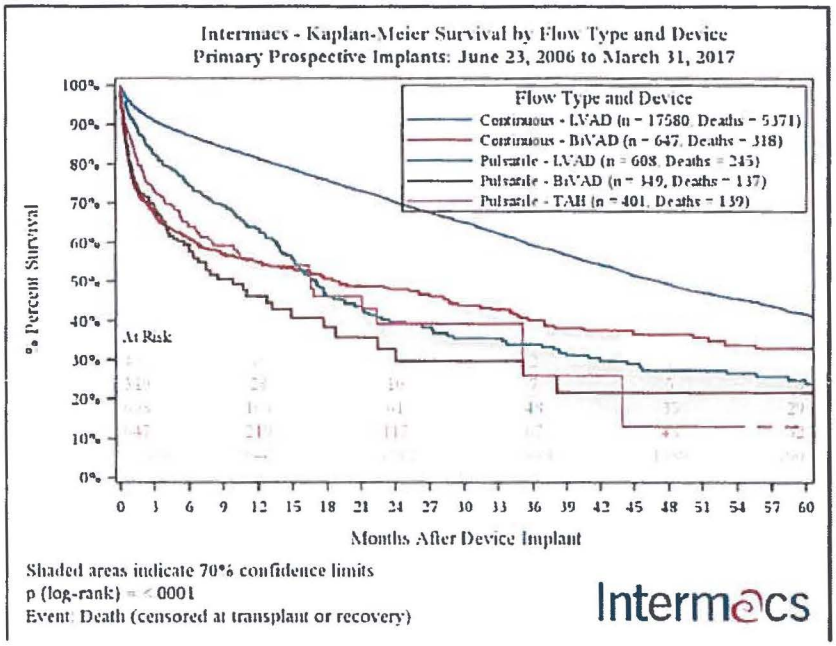

Recent studies have found that the left ventricular assist device (LVAD) is not the final solution for many patients with failing myocardium; the reported incidence of right ventricular failure after LVAD placement ranges from 9 to 30%.[12] Moreover, when complete biventricular failure occurs, VADs are ineffective and can pose a risk to the patient in terms of complications, as detailed in Section III(B) below. For that group of patients with irreversible biventricular failure, replacement of total heart pump function is needed. It is for this situation that a biventricular replacement device, the TAH-t, was developed.

In the ten years since CMS issued an NCD with CED for artificial hearts, advances in the technology combined with published literature on larger and more diverse patient populations demonstrate the importance of the TAH-t in the treatment of patients with biventricular failure. In the 2008 NCD, CMS called for continued evidence development to address certain questions about the health benefits of artificial hearts, with a focus on published literature to confirm that outcomes achieved in initial smaller scale studies could be extrapolated to larger patient populations and to confirm the longevity and survival rates associated with artificial hearts. Recently, Francisco A. Arabia et al. completed a comprehensive, multi-institutional registry study ("Arabia-Intermacs Study") on the TAH-t and found that, although the patient population who receive TAH-t tend to be sicker than the population on LVAD support, over 53% of the 450 patients who have received a TAH-t survived to heart transplantation within 12 months and another 13% continued to survive on the TAH-t at the twelve month mark.[13] Thus, at one year, 66% of patients who were previously facing certain death and received the TAH-t were alive – most of whom had received a heart transplant by then, but some of whom remained on the TAH-t. The longest duration of TAH-t support has been achieved by a patient who just turned

12 Arabia-Intermacs Study at 1305.
13 *Id.*

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65 and remains on support after more than five years. Moreover, advances to the TAH-t technology increases patient mobility with the device, allows the patient to be discharged (which reduces in-hospital costs), and with the introduction of the 50cc TAH-t, it allows greater flexibility in device size for a more diverse patient population. Collectively, these developments merit CMS reconsidering the artificial heart NCD to remove the CED condition for coverage of the 70cc TAH-t when used as a bridge to transplant.

I. Description of the TAH-t

The TAH-t is an implantable artificial heart. The TAH-t is a pulsating bi-ventricular device that is implanted into the chest to replace the patient's left and right ventricles, and then sewn to the patient's remaining atria. The TAH-t is then connected by tubes through the patient's chest wall to a driver, which operates the device and indicates cardiac output and alarms, if changes in the driver or patient condition will affect continued operation.

Through the premarket approval process, the TAH-t is approved by the Food and Drug Administration (FDA) for use as a bridge to a heart transplant for transplant-eligible patients at risk of death from biventricular failure. In addition, the FDA has granted the 70cc TAH-t an Investigational Device Exemption (IDE) for use as "destination therapy," i.e., indefinitely, for patients who are ineligible for a heart transplant. Below is a summary of the FDA approval status of the various forms of the TAH-t.

TAH-T	**FDA Status**
70cc Bridge to Transplant	PMA Approved: October 15, 2004
C2 Driver System	PMA Approved: May 16, 2012
Freedom Driver System	PMA Approved: June 26, 2014
70cc Destination Therapy (patients not eligible for cardiac transplant with BSA $\geq 1.7m^2$)	HUD Approval: March 2, 2012
70cc Destination Therapy Study (adult patients not eligible for cardiac transplant with BSA > 1.7m2)	IDE Approval: March 6, 2015
50cc Bridge to Transplant (pediatric patients with BSA 1.2-1.7m^2)	HUD Approval: January 30, 2013
50cc Bridge to Transplant IDE Studfy (pediatric and adult patients)	IDE Approval: March 20, 2015
50cc Destination Therapy	HUD Approval: January 15, 2013

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The TAH-t System is composed of implantable artificial ventricles and valves that replace the native anatomy and are connected by drivelines to an external pneumatic, pulsatile driver. Commercially available, continuous flow, durable circulatory assist devices (VADs) in the bridge-to-transplant category use mechanical assistance to facilitate circulation of the blood with the heart still in place. From a clinical perspective, the TAH-t is unique and is distinguished from VADs because it is the only mechanical circulatory device that allows for complete control of blood circulation and is indicated when the patient is at imminent risk of death from biventricular failure. The clinical distinctions among mechanical circulatory devices for patients suffering from biventricular failure are discussed in Section III(B) below.

A. The TAH-t Device

The design of the TAH-t arose from the clinical need for a system capable of completely restoring systemic and pulmonary blood circulation and organ perfusion pressure in patients with failed circulatory systems resulting from irreversible biventricular dysfunction.[14]

The TAH-t is an orthotopic, pneumatically-driven, pulsatile pump, consisting of two separate polyurethane chambers that replace the patient's native diseased ventricles and valves (**Figure I-1** below). There are two available sizes for the chambers, the standard 70cc chamber that is the primary focus of this request and a smaller 50cc chamber that is the subject of an ongoing IDE clinical trial.[15] The patient's total cardiac output is provided by the TAH-t, which pumps blood through both the pulmonary and systemic circulations. For the larger 70cc chambers, the maximum measured cardiac output is 10.5 liters per minute, which is one of the highest cardiac volumes provided by any mechanical circulatory assist device.[16] The beat rate can be set to meet the unique cardiac output needs of each patient.

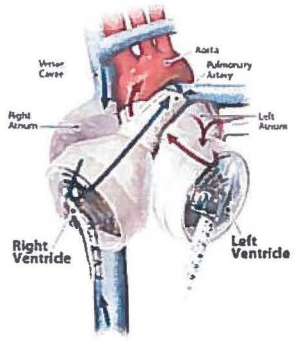

Figure I-1. Photograph of TAH-t with Cannulae

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14 Slepian, M., et al., "The SynCardia CardioWest™ Total Artificial Heart," *Treatment of Advanced Heart Disease,* Taylor & Francis Group (2006), 473-90, at p. 474.

15 *SynCardia 50cc TAH-t as a Bridge to Transplant*, NCT02459054, https://clinicaltrials.gov/ct2/show/NCT02459054.

16 Copeland, J.et al., *Total artificial hearts: Bridge to transplantation*, 21 Cardiology Clinics 101, 111 (2003).

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The 50cc chamber, in particular, makes the device available to a more diverse patient population. In the Arabia-Intermacs Study, 87% of the 450 patients receiving the 70cc TAH-t from June of 2006 to April of 2017 were men. A significant contributor to that statistic is the size of the 70cc TAH-t and the inability to accommodate the device in the chest cavity of small statured adults, particularly women. Thus, the decreased size of the 50cc TAH-t makes this technology increasingly available to women, evidenced by the fact that 61.5% of the patients enrolled in the ongoing 50cc TAH-t study are women. As of February 2019, 53% of 50cc TAH-t patients implanted globally are women.

Each artificial ventricle consists of a semi-rigid polyurethane shell that houses four flexible polyurethane diaphragms. These diaphragms allow the blood chamber of the ventricle to fill passively and then eject blood when the diaphragms are compressed by air that is pumped into the air chamber side of the diaphragms by the external driver. Drivelines connect the pneumatic output of the external driver to the TAH-t cannulae. Where the cannulae traverse the chest wall, a 9.75" length of velour covers the external surface to promote tissue adherence and minimize the risk of infection. SynHall mechanical heart valves (2014 to the present) are mounted in the inflow (27mm diameter) and outflow (25mm diameter) ports of each artificial ventricle, and control the direction of blood flow.

The surgical implantation procedure includes removal of the patient's native ventricles and valves. Two inflow connectors are then sewn onto the native atria, two outflow connectors are sewn onto the pulmonary artery and aorta, and the artificial ventricles are inserted. The cannula for each artificial ventricle is tunneled sub-diaphragmatically and exits the patient's skin below the ribs on the left side to connect to seven-foot drivelines that are coupled to the back of the pneumatic driver (**Figure I-2** below). The method of using the TAH-t is similar to heart transplant except that the atria are left in place. Therefore, surgeons who are experts in complex cardiac procedures and other transplant team members who are experienced in caring for patients on mechanical circulatory assist devices are able to understand the differences in the use of the total artificial heart. SynCardia provides a rigorous, multi-phase training program to assure that the implant team is exceptionally well prepared to use the device.

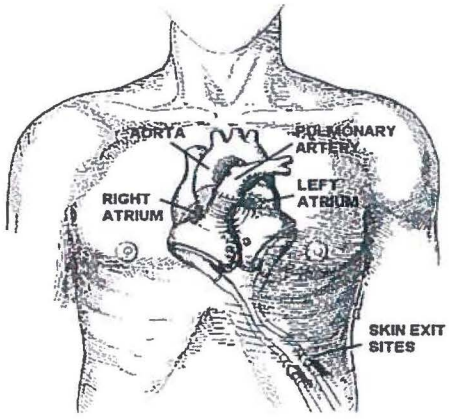

Figure I-2. Placement of TAH-t

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B. External Drivers

1. Companion 2 Driver System

Upon implantation in the hospital and for the duration of the inpatient stay, the TAH-t is run by a hospital driver, called the Companion 2 (C2) Driver System, that is provided by SynCardia to the hospital and used for different patients (at different times) in the inpatient setting. The C2 Driver is only for hospital use and is not taken with the patient when leaving the hospital on TAH-t support.

The C2 Driver System connects to the TAH-t and generates and controls the pulses of air that cause the TAH-t diaphragm to move. It weighs 70 pounds and includes a liquid crystal display (LCD) screen that is intended to allow for appropriate monitoring of device function. The color touch screen LCD is the main user interface and provides numerous capabilities including

- Adjustment of rate, percent systole, left and right drive pressure, and left and right vacuum;
- Patient file set-up;
- Display of alarms, review of alarm status; and
- Graphical display of pressure, flow, and average cardiac output for both left and right ventricles.

The C2 Driver docks in the Hospital Cart and provides a stable support mechanism with wheels for patients to lean on and walk around the hospital with appropriate staff. It is designed for use in the hospital to facilitate monitoring of the device function during the implant procedure and in the Intensive Care Unit (ICU). The Hospital Cart includes a 15 inch LCD monitor designed for input and output with touch screen capability to enter patient and facility information and make necessary adjustments. The C2 Driver can also be docked in a Hospital Caddy, which is a smaller mobile cart with wheels which allows ambulation in stable patients inside and around the hospital. This configuration replaced the original driver system (the Circulatory Support System Console), which is in the process of being obsoleted and is currently not in the field.

2. Freedom Driver System

Typically, at some point after the TAH-t is implanted, the patient has recovered sufficiently to be discharged from the hospital. At that point, the patient no longer needs the higher level of functioning necessary for recovery that the C2 Driver affords, and instead can be fully supported by a smaller driver, the Freedom Driver, which can be carried in a backpack or shoulder bag. The Freedom Driver System was FDA-approved in June 2014.

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Prior to discharge, the patient is transitioned in the hospital from the C2 Driver to the Freedom Driver. At that time, the patient receives two Freedom Drivers – the primary driver that must be connected to the TAH-t continuously, and a backup driver in the event of a failure of the primary driver (as a patient cannot survive without a functioning driver). In addition to the Freedom Drivers themselves, the patient also receives the other external components related to the TAH-t, including batteries to power the drivers, power cords, battery charger and custom backpack, shoulder bag and accessory bag (which allows the patient to keep both drivers, extra batteries and accessories nearby at all times, to ensure survival). The primary Freedom Driver needs to be serviced about every 120 days. At that time, the patient will return to the hospital to switch from the primary driver to the backup driver, and a new backup Freedom Driver will be provided. The unit which had been the primary Freedom Driver will be sent to SynCardia for servicing and returned into circulation.

II. Description of the Proposed Use of the Item or Service

A. Indication for Use

Pursuant to its FDA label, the TAH-t is a biventricular replacement device that is indicated for use as a bridge to transplantation in cardiac transplant-eligible candidates at risk of imminent death from biventricular failure. Biventricular failure can result from ischemic myopathy, dilated myopathy, valvular heart disease, refractory arrhythmias, adult congenital heart disease, failed transplant, failed VAD support, ventricular rupture, cardiac arrest and cardiac malignancies, all of which lead to end stage, or terminal, heart failure. The Instructions for Use are attached as **Tab 3**, and the Summary of Safety and Effectiveness is attached as **Tab 4**. The 50cc TAH-t is being studied in an Investigational Device Exemption (IDE) trial for the same indication.

In addition, the FDA has granted the TAH-t an IDE for use as "destination therapy," i.e., indefinitely, for patients who are ineligible for a heart transplant. The artificial heart NCD authorizes Medicare coverage of the TAH-t as destination therapy through CED and CMS approved a SynCardia destination therapy study for the TAH-t in March of 2015. The destination therapy study continues to enroll patients, and experience with patients in the study has revealed beneficial impacts, including patients who are in the destination therapy study because they are not clinically eligible for a heart transplant but who have recovered while on the TAH-t to the point that they become eligible for a heart transplant. As such, they convert from a destination therapy patient to a bridge to transplant patient under the study.

B. Medical Conditions for Which the Device Can be Used

As noted earlier, the 70cc TAH-t is indicated for patients with biventricular failure who are awaiting a donor heart. Any generalized decline in heart pump function has been termed "heart failure." The term congestive heart failure, or CHF, further encompasses the effects of this failed cardiac performance in terms of its impact on the body.

A decline in cardiac function, with reduced left ventricle forward output, results in organ and whole body under-perfusion. Similarly, the lack of emptying of the right ventricle, with a

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backward pressure build-up, results in increased pressure and movement of fluid out of vessels and into tissues, including the lung, liver, abdomen and extremities. This effect results in edema and many of the "congestive" symptoms, including shortness of breath, abdominal and leg swelling and worsening renal function. CHF may occur either progressively or acutely, depending upon the underlying etiology of cardiac function decline. As the severity of CHF increases, the rate of decline often accelerates. Congestive heart failure is commonly regarded as the "final common pathway" of all forms of heart disease. However, depending on etiology, some patients require TAH-t intervention even before experiencing CHF.

C. Target Medicare Population

The target population for use of the TAH-t as a bridge to transplant includes beneficiaries entitled to Medicare on the basis of age and disability. Heart failure is primarily a disease of the elderly but affects people of all ages, from children and young adults to the middle-aged and the elderly. In the Medicare aged population, the prevalence of CHF is 6-10%, compared to less than 2% in patients younger than 65.[17] Approximately 71% of patients requiring hospitalization for CHF are of Medicare age.[18] Only when these beneficiaries are in biventricular failure and are at imminent risk of death would they be in the target Medicare population for the TAH-t.

Patients younger than 65 years of age may also qualify as Medicare and/or Medicaid beneficiaries when they have been diagnosed with advanced or end-stage heart failure. These patients are disabled by refractory heart failure that requires specialized interventions. These patients have marked symptoms at rest despite maximal medical therapy and are often recurrently hospitalized or cannot be safely discharged from the hospital without a heart transplant, chronic inotropes, permanent mechanical support or experimental surgery or drugs.[19] The TAH-t System is indicated for a defined group of this heart failure population, regardless of age, with HF from varied etiologies or end-stage CHF who are eligible for and in imminent need of a heart transplant.

Even though patients may be implanted while covered by private insurance, they may become Medicare and/or Medicaid patients during TAH-t support. Eligibility may occur because of reaching the age of 65, financial hardship, changes in marital status or becoming eligible for Medicare disability.

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17 Emory Healthcare Health Connection, Heart & Vascular: Conditions & Treatments, Heart Failure Statistics (https://www.emoryhealthcare.org/heart-vascular/wellness/heart-failure-statistics.html) (last visited 4/25/19).

18 National Center for Health Statistics, Hospitalization for Congestive Heart Failure: United States, 2000-2010 (October 2012) (https://www.cdc.gov/nchs/products/databriefs/db108.htm).

19 American College of Cardiology Foundation and American Heart Association, Inc. (2005), *ACC/AHA 2005 Guideline Update for the Chronic Diagnosis and Mgt. of Heart Failure in the Adult*, at p. 8.

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D. The TAH-t Fulfills a Role that Other Mechanical Circulatory Support Devices Cannot

Surgeons today have a number of choices with respect to mechanical circulatory support assist devices, including ventricular assist devices (VADs), that can be effective in bridging terminal heart failure patients to transplantation,. While these devices are beneficial for many patients, they carry significant risks and are contraindicated for those in irreversible biventricular failure. Despite the limitations of VADs, they may be utilized for patients in biventricular failure because of the lack of other treatment options, or difficulties associated with enrolling in clinical trials in order to be eligible for Medicare coverage of the TAH-t. As explained in Section III(B), the TAH-t has many distinct advantages over VADs as a bridge to transplant in patients with biventricular failure, fulfilling a role that no other mechanical circulatory support device can.

E. Implant Centers

A critical part of the successful use of the TAH-t is the selection of the institutions at which the device will be implanted. The TAH-t is made available only to implant centers that meet rigorous eligibility criteria and participate in a comprehensive certification program.

1. Current Implant Centers

The TAH-t System is available worldwide at over 140 certified centers in 20 countries. In the United States, it is available at over 65 major transplant institutions (and one institution associated with a transplant center, but that is only a certified VAD destination center), which are in the attached list in **Tab 5**. All of these centers have been approved by CMS as meeting facility standards for adult heart transplantation and/or for use of VADs as destination therapy.

2. Criteria Used for Implant Center Selection and Implementation

The careful selection of leading transplant institutions (or as appropriate, VAD destination centers affiliated with a transplant program) to participate in the SynCardia TAH-t program, and the ongoing rigorous certification and qualification of those institutions by SynCardia contribute significantly to the clinical success demonstrated by the TAH-t System. Each institution participating in the SynCardia program was selected, and would be selected, because of its capacity to be able to support the program and its high level of proficiency in doing so.

Inclusion in the SynCardia program builds upon an institution's approval by CMS as an adult heart transplant center and/or as a VAD destination therapy facility.

3. Certification

The Initial Start-Up Certification consists of a multi-phase program which is intentionally rigorous, with on-going training provided by SynCardia. The certification program includes recommendations for anticoagulation as well as recommendations for TAH-t patient management and many other elements that work together to provide good patient outcomes. In

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addition, the curriculum employs a patient simulator (purchased by the hospital as part of the new center start-up kit) that allows hospitals to develop their skills before encountering their first TAH-t implant. Product manuals are available electronically and in print to all TAH-t certified centers.

Each hospital participating in the SynCardia Program expends significant resources, including a training fee, for certification-related activities over the four part certification program. These certification-related resource expenditures create a "self-sorting mechanism" that selects only those hospitals that are willing to make a significant commitment to be a participant in the SynCardia Program. A detailed description of the certification program and the SynCardia Manuals are available upon request.

III. Evidence Demonstrating Improved Health Outcomes

This section addresses the clinical and scientific evidence demonstrating improved health outcomes from the 70cc TAH-t when used as a bridge to transplantation in cardiac transplant-eligible terminal heart failure patients at risk of imminent death from biventricular failure when ventricular assist devices are contraindicated or insufficient. These data are relevant to the national coverage determination because they demonstrate that additional scientific evidence that was not available for the original consideration of the artificial heart NCD more than 10 years ago demonstrate positive patient outcomes across diverse clinical sites and diverse patients that support coverage of the 70cc TAH-t as a bridge to transplant under section 1862(a)(1)(A) of the SSA.

In the current NCD for artificial hearts, CMS raised three questions underlying the request for additional evidence development prior to granting full coverage. These questions were:

1. Were there unique circumstances such as expertise available in a particular facility or an unusual combination of conditions in particular patients that affected their outcomes?
2. What will be the average time to device failure when the device is made available to larger numbers of patients?
3. Do results adequately give a reasonable indication of the full range of outcomes (both positive and negative) that might be expected from more widespread use?

The literature described in this reconsideration request demonstrates that the studies conducted in the past ten years have provided satisfactory answers to these questions, such that CMS may remove the requirement for study participation from the NCD. As will be addressed in further detail below, the Arabia-Intermacs Study in particular demonstrates that successful patient outcomes were obtained across a large patient population, see Section III(A)(3)(a), and that were consistent, with some variations based on experience, across facilities, see Section III(A)(3)(b). Moreover, as Section III(A)(3)(c) explains, although the study found high rates of device malfunctions related to the frequent required changes to the Freedom Driver, around 13% of patients remained alive on the device twelve months after implantation on top of the 53% of patients that were successfully bridged to a transplant during that period while using the TAH-t.

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The purpose of a bridge to transplant device is to hemodynamically stabilize transplant eligible patients when they reach the point that their native heart is functioning so poorly that they may experience irreversible end-organ damage to kidneys, brain, etc. In order for these patients to have the chance of benefiting from the heart transplant for which they are eligible, the intermediate step of providing them with mechanical circulation is necessary. The long term safety and efficacy of heart transplantation is well accepted. Therefore, the outcome that reflects a safe and effective bridge to transplant technology would be one that provides safe and effective mechanical support long enough to allow a substantial fraction of the patients receiving this device to receive a heart transplant. As the Arabia-Intermacs Study found, 53% of patients survive on the TAH-t and receive a heart transplant within twelve months after implantation of the device and another 13% remain alive on the TAH-t twelve months after implantation, continuing to wait for a heart transplant.

Furthermore, it is significant that during the period of mechanical support, there is hemodynamic improvement that is sufficient to reduce or eliminate end organ damage and other potentially irreversible effects of end-stage heart failure. It is important to keep in mind that for patients who are transplant eligible, the primary purpose of the SynCardia device is as a bridge to transplant, not as an alternative to transplant, and in that sense the measures that are relevant to assessing whether it improves health outcomes in Medicare beneficiaries are whether it is clinically superior to the alternative – which is waiting for a heart transplant with a different type of mechanical assistance, or in the state of severe hemodynamic compromise offered by their failing native heart.

A. Arabia-Intermacs Study

As previously mentioned, Francisco A. Arabia et al. recently completed a large scale analysis of registry data related to survival, adverse events, and competing outcomes for 450 patients available in the Intermacs database. The population studied represents all patients 19 years of age and older that received the 70cc TAH-t as a bridge to transplant from June 23, 2006 to April 30, 2017 and for whom data were entered into the Registry (79% of TAH-t implants in the US during that period). The text of this peer-reviewed study published in the *Journal of Heart and Lung Transplantation* is provided in **Appendix III-A**.

1. Study Objective

The primary aim of the study was to determine the patient characteristics and survival outcomes of the TAH-t with current technology, and to determine risk factors and document adverse events for patients who received a TAH-t.

2. Study Design

As noted, the study examined Intermacs Registry data from patients aged 19 years and older who received the 70cc TAH-t as a bridge to transplantation or candidacy over about an 11 year period beginning in June of 2006. The Data Coordinating Center at the University of Alabama performed the data analysis. Patient condition at implant was categorized according to the Intermacs Patient Profiles (IPP).

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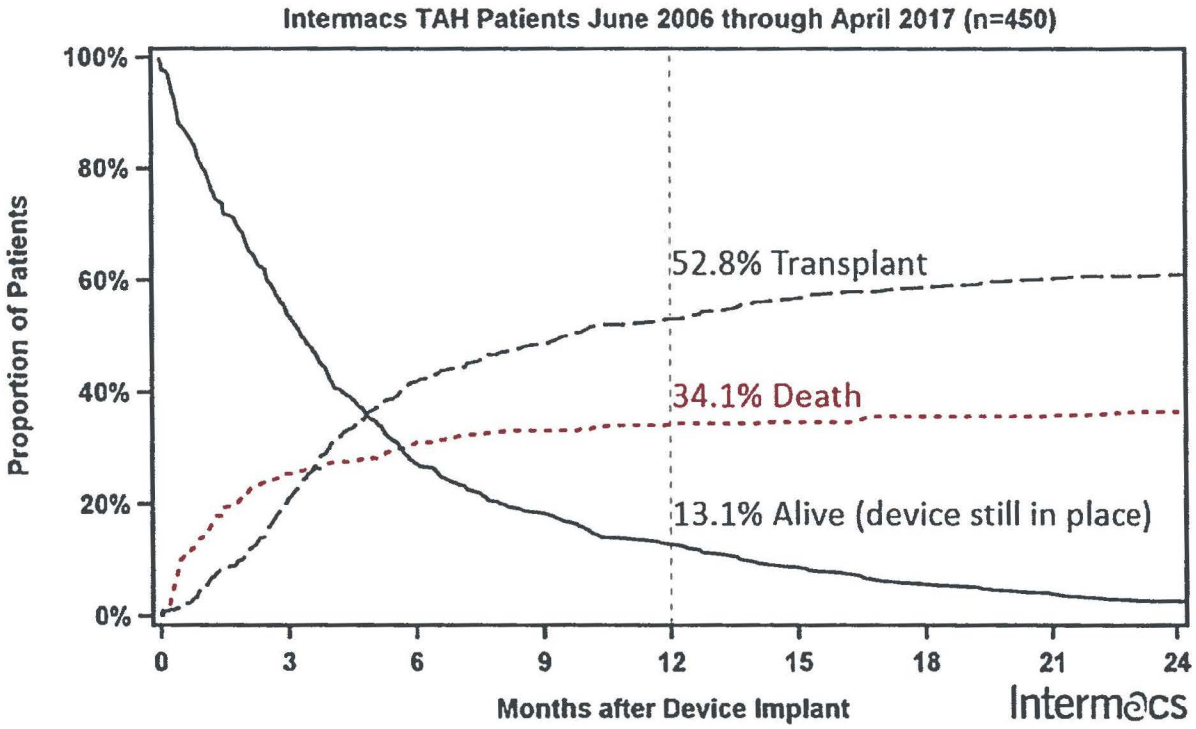
3. Study Results

Complete follow-up data were available from 450 patients who underwent TAH-t implantation during the period of the study. The patients were primarily men (87%) and, on average, 50 years old (range, 19-72 years). More than 95% of the patients were on the active list for a heart transplant or underwent TAH-t as a bridge to candidacy.

a. Patient Outcomes

The Arabia-Intermacs Study provides a clear answer to the third question raised by CMS regarding the full range of outcomes that might be expected from widespread patient use: 53% of patients with severe biventricular failure who receive the TAH-t survive to transplantation within 12 months after implantation. Further, about two-thirds of patients with severe biventricular failure remain alive at one year – 53% are transplanted and 13% remain alive on the TAH-t. Overall, the study found that, of the 450 patients, transplantation was performed in 266 patients, 22 patients were alive on device and 162 patients died on support. By competing outcome analysis in the graph below, the overall rate of transplantation was 53%, mortality was 34%, and 13% of patients were alive on a device by 12 months.[20] Therefore, 66% of TAH patients were either alive on device or had been transplanted by 12 months. The most common cause of death was multisystem organ failure (36%), followed by neurologic injury (18%), and elective withdrawal of support (12%).



[20] Arabia-Intermacs Study at 1306.

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b. Variations Across Facilities

Arabia et al. further found that the TAH-t was successful for patients at a variety of facilities, which responds to the first question raised by CMS, although the study also found that centers with more experience had higher rates of favorable outcomes; the 12-month survival was 64.8% for centers with more than 10 implants as compared to 36.7% for centers with 10 or fewer. Centers implanting more than 10 TAH-t during the study period also performed more heart transplantations within 12 months (58.4%) as compared to 43% in lower-volume centers. The study conjectured that improvement in TAH-t survival in high volume centers could be the result of surgical experience with device implantation, a better understanding of patient selection, the timing of intervention, and patient management. It should be noted that currently, of the 79 implanting centers in the United States, 21 centers have performed more than 10 implants. Thus, it is clear that the TAH-t can be successfully utilized in numerous facilities in the United States.

c. Device-Related Adverse Events

With regard to the second question CMS raised regarding time to device failure, the Arabia-Intermacs Study identified rates of device malfunction, but found the device remained viable in all patients who did not receive a transplant but remained alive on device support at the twelve month mark (13%). Specifically, the Arabia-Intermacs Study found at the three month mark, minor device malfunction and infection were the most prevalent adverse events. At six months, the incidences of major and minor device malfunction were 7.1% and 28.2%, respectively. However, the study also found that the device malfunction rate was high in the period of 3 to 24 months because of minor malfunctions resulting in Freedom Driver exchanges, not because of pump-component failure or thrombosis. Moreover, the Intermacs database reported a very low percentage (3.1%) of patient deaths caused by device malfunction. These data, combined with the study's finding that, after twelve months, 13.1% of patients remained alive on the device while 52.8% of patients had received a heart transplant, demonstrate that device implantation into a large number of patients did not identify significant device failure concerns.

4. Study Conclusions

The Arabia-Intermacs Study found, consistent with the TAH-t's indication for severe biventricular failure, patients who received a TAH-t were generally sicker than patients who elected other treatment options such as the LVAD. At the time of implantation, 80% of the patients were designated IPP stage 1 (critical cardiogenic shock) or 2 (progressive decline); patients who received LVADs were more frequently designated IPP stage 2 and 3 (stable but inotrope dependent). The study also found that 82% of patients had baseline characteristics that describe right ventricular (RV) failure at the time of implant, including dialysis, ECMO, ventilator support-dependent, severely reduced RV ejection fraction, temporary MCS, or moderate or severe tricuspid valve insufficiency. The study concluded that there continue to be challenges for providers determining appropriate timing of referral and intervention with LVAD, which may factor into patients who subsequently develop RV dysfunction requiring a TAH-t. Nonetheless, the authors concluded that the encouraging survival of patients with unrecognized

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RV failure with the TAH-t provides support for consideration of the TAH as an alternative for LVADs in patients with severe biventricular failure.

B. Biventricular Replacement Devices vs. Ventricular Assist Devices

The therapeutic approach for the use of mechanical circulatory assist devices in terminal heart failure patients has been to maximize cardiac output to both improve pressure and flow to end organs, and to increase "washing" of the blood contacting surfaces, thus reducing the risk of thromboembolism.[21]

Use of the TAH-t, unlike the use of VADs for patients with biventricular failure, improves outcomes in dying patients by providing immediate hemodynamic restoration and clinical stabilization, leading to end organ recovery and thus eventually allowing cardiac transplantation.[22] The TAH-t replaces both ventricles of the heart orthotopically, and as a result, there is no concern about right heart failure, pulmonary hypertension, valve issues or arrhythmias, as with VADs.[23] The TAH-t patient no longer has heart disease.

The TAH-t System can predictably lower filling pressures and produce higher perfusion pressure, resulting in improved end-organ perfusion. Most importantly, it reliably provides one of the highest cardiac volumes (flows of up to 10.5 liters per minute) of any VAD or biventricular assist devices (BiVAD). The flow limitation, always an issue with extracorporeal BiVADs and seen in cases of right ventricular failure with LVADs, is not present with the TAH-t. In addition, mean arterial pressures with the TAH-t System are usually in the 70-90 mmHg range, resulting in a perfusion pressure of 55 to 80. Delivery of this magnitude of pressure and flow has resulted in consistent return of renal, hepatic and other end-organ function to normal, even in the sickest of patients.[24]

The TAH-t also obviates many limitations that are associated with VAD-mediated cardiac support. Leaving the ventricles intact in the end-stage CHF patient, as occurs when a VAD is utilized, often turns out to be a major liability for the patient, as the major cause of cardiac failure in patients supported with LVADs is eventual right heart failure.[25] Placement of a second VAD as an RVAD carries a high morbidity and mortality with significantly reduced bridge to transplant success.

Recent studies have found that the TAH-t is a necessary and important alternative treatment option for patients with biventricular failure. Allen Cheng, et al. conducted a study review of adult heart transplantation patients from January 2005 to December 2014 in the United Network of Organ Sharing (UNOS) database who were supported with either the TAH (212

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21 Copeland, G. et al., *supra* note 16 at 105.
22 Copeland, G. et al., *supra* note 9 at 865.
23 Copeland, G. et al., *supra* note 16 at 105.
24 *Id.* at 104.
25 Wang, Y. et al., *Decision tree for adjuvant right ventricular support in patients receiving a left ventricular assist device*, 31 J. Heart & Lung Transplantation 140 (2012).

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patients) or biventricular ventricular assist devices (BiVAD) (366 patients).[26] The authors concluded that no statistical significance ($p = 0.1$) in the post-transplant survival was observed between the two cohorts. The 30-day, one-, and three-year post-transplantation survival was 88%, 78%, and 67%, respectively, for patients with TAH support versus 93%, 83%, and 73% for patients with BiVAD support. Consistent with the Arabia-Intermacs Study, the authors also observed that the patient population who selected TAH was sicker than the group that received BiVAD support. Ultimately, the study found that there was no difference in wait-list survival in patients supported with TAH-t or BiVAD.

C. UNOS Donor Heart Allocation Rules

UNOS issued new organ allocation rules for heart and heart-lung recipients that went into effect in September and October 2018. The revised allocation rules classify all adult TAH-t patients as UNOS Status 2, regardless of discharge status. This revision will most likely result in wait time reductions for TAH-t patients, as the previous UNOS allocation rules downgraded the status of TAH-t patients upon discharge from the hospital. In most cases, TAH-t patients who become clinically stable are discharged, whereas Status 2 patients on biventricular support by other eligible mechanical circulatory support devices (MCSDs) typically remain hospitalized. The ability to retain Status 2 classification in the out-of-hospital environment optimizes the TAH-t as a treatment option.

In addition, the revised UNOS allocation rules narrowed the set of adult patients who are classified as Status 1 which will ultimately impact the wait times of patients classified as Status 2. Patients on extracorporeal membrane oxygenation (ECMO) will be downgraded from Status 1 to Status 3 after seven days and LVAD patients will be downgraded to Status 4 (after a discretionary 30 days at Status 3).

IV. Conclusion

Much has changed in the 10 years since the original consideration for the artificial heart NCD and the CMS determination that the evidence did not support coverage under section 1862(a)(1)(A) of the Social Security Act, but rather under CED. The number of United States centers utilizing the TAH-t successfully has increased more than four-fold (from 9 to 68). More importantly, the scientific evidence related to the 70cc TAH-t as a bridge to transplant now supports coverage under section 1862(a)(1)(A) of the Social Security Act. The evidence shows that the 70cc TAH-t as a bridge to transplant improves health outcomes for Medicare beneficiaries with biventricular failure at imminent risk of death awaiting heart transplant, as it enables a substantial fraction of these beneficiaries to survive long enough to receive their transplant. The 70cc TAH-t also improves health outcomes by making these patients better candidates for transplantation because of the immediate and sustained improvement in their hemodynamic variables. In the past ten years since CMS granted coverage with evidence development for artificial hearts, there have been multiple peer-reviewed, published studies providing adequate evidence that the TAH-t improves health outcomes when used as a bridge to

[26] Cheng, A. et al., *Comparison of total artificial heart and biventricular assist device support as bridge-to-transplantation*, 31 J. Cardiac Surgery 648 (2016).

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transplantation in cardiac transplant-eligible heart failure patients at risk of imminent death from biventricular failure. The ending of several CMS-approved studies of the TAH-t, in particular of the more commonly used 70cc TAH-t, could leave beneficiaries without access to the TAH-t in the near future. Therefore, we believe that CMS should conclude that this device is reasonable and necessary for this indication and issue a favorable coverage decision for this biventricular replacement device, unencumbered by the existing requirement for evidence development.

We appreciate your consideration of this request. Please do not hesitate to contact me (520-545-1234, or jskroback@syncardia.com) or Stuart Langbein of Hogan Lovells (202-637-5744, or stuart.langbein@hoganlovells.com) with any questions. We look forward to working with you on a reconsideration of the artificial heart NCD.

Sincerely,

Judy Skroback

Judy Skroback
Director of Clinical Research
SynCardia Systems, LLC

cc: Stuart Langbein (Hogan Lovells)

Attachments

TAB 1

ELSEVIER

The Journal of
Heart and Lung
Transplantation
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FEATURED PAPERS

Interagency registry for mechanically assisted circulatory support report on the total artificial heart

Francisco A. Arabía, MD, MBA,[a] Ryan S. Cantor, PhD,[b] Devin A. Koehl, BS,[b] Vigneshwar Kasirajan, MD,[c] Igor Gregoric, MD,[d] Jaime D. Moriguchi, MD,[e] Fardad Esmailian, MD,[a] Danny Ramzy, MD, PhD,[a] Joshua S. Chung, MD,[a] Lawrence S. Czer, MD,[e] Jon A Kobashigawa, MD,[e] Richard G. Smith, MSEE, CCE,[f] and James K. Kirklin, MD[b]

From the [a]Cardiothoracic Surgery Division, Cedars-Sinai Medical Center, Los Angeles, California; [b]Kirklin Institute for Research in Surgical Outcomes, University of Alabama at Birmingham, Birmingham, Alabama; [c]Department of Surgery, Virginia Commonwealth University Health System, Richmond, Virginia; [d]Center for Advanced Heart Failure Program, University of Texas Health Science Center Houston, Houston, Texas; [e]Cardiology Division, Cedars-Sinai Medical Center, Los Angeles, California; and the [f]Artificial Heart and Perfusion Programs, Banner University Medical Center, Tucson, Arizona.

KEYWORDS:
total artificial heart;
mechanical circulatory support;
INTERMACS;
biventricular failure;
bridge to transplantation

BACKGROUND: We sought to better understand the patient population who receive a temporary total artificial heart (TAH) as bridge to transplant or as bridge to decision by evaluating data from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) database.

METHODS: We examined data related to survival, adverse events, and competing outcomes from patients who received TAHs between June 2006 and April 2017 and used hazard function analysis to explore risk factors for mortality.

RESULTS: Data from 450 patients (87% men; mean age, 50 years) were available in the INTERMACS database. The 2 most common diagnoses were dilated cardiomyopathy (50%) and ischemic cardiomyopathy (20%). Risk factors for right heart failure were present in 82% of patients. Most patients were INTERMACS Profile 1 (43%) or 2 (37%) at implantation. There were 266 patients who eventually underwent transplantation, and 162 died. Overall 3-, 6-, and 12-month actuarial survival rates were 73%, 62%, and 53%, respectively. Risk factors for death included older age ($p = 0.001$), need for pre-implantation dialysis ($p = 0.006$), higher creatinine ($p = 0.008$) and lower albumin ($p < 0.001$) levels, and implantation at a low-volume center (≤10 TAHs; $p < 0.001$). Competing-outcomes analysis showed 71% of patients in high-volume centers were alive on the device or had undergone transplantation at 12 months after TAH implantation vs 57% in low-volume centers ($p = 0.003$).

CONCLUSIONS: Patients receiving TAHs have rapidly declining cardiac function and require prompt intervention. Experienced centers have better outcomes, likely related to patient selection, timing of implantation, patient care, and device management. Organized transfer of knowledge to low-volume centers could improve outcomes.

J Heart Lung Transplant 2018;37:1304–1312

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See Related Editorial, page 1298

1053-2498/
https://doi.org/10.1016/j.healun.2018.04.004

Physicians, engineers, scientists, and even science fiction writers had long pondered the idea of replacing the human heart with an artificial pump, but it was not until 1935 that aviator Charles Lindbergh and Nobel laureate Alexis Carrel designed the first prototype[1] made entirely of hand-blown glass. Subsequently, numerous models of total artificial hearts (TAHs) have been designed and even implanted—many of which preceded the development of the left ventricular assist device (LVAD)—but only the pneumatic pulsatile TAH has been widely used.[2–7]

Throughout the world, the continuous-flow (axial or centrifugal) LVAD is the primary long-term mechanical circulatory support (MCS) for patients with severe congestive heart failure, as either a bridge (to transplant or decision) or destination therapy. However, the LVAD is not the final solution for many patients with failing myocardium. The reported incidence of right ventricular (RV) failure after LVAD placement, even with the use of newer LVAD models, ranges from 9% to 30%,[8,9] which results in prolonged inotrope dependence or the need for short-term or long-term MCS. RV failure has a negative effect on patient survival,[10] but identifying reliable predictors of which patients will develop RV failure has proven elusive.[11–16] No single parameter is sufficient to predict RV failure before or after LVAD implantation.[17]

Comparison of results from LVADs and biventricular assist devices (BiVADs) have suggested that the patient's condition at implantation rather than device technology may dominate the calculus of inferior survival with biventricular support.[18,19] However, TAHs and BiVADs have different profiles of survival and are associated with different adverse events (AEs). Others showed that survival rates were higher in patients who had a TAH implanted compared with patients who received support from implantable or paracorporeal BiVADs for longer than 90 days.[20] There has never been a TAH randomized trial.

The primary aim of this study was to determine the patient characteristics and survival outcomes of the TAH with current technology. We also sought to determine risk factors and document AEs for patients who received a TAH.

Methods

Intermacs

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) database represents a public-private partnership among the National Heart, Lung, and Blood Institute, hospitals, and industry. Before data collection began on June 23, 2006, 53 institutions received Institutional Review Board approval to participate in the INTERMACS Registry and subsequently contributed data to the registry. The Data Coordinating Center at the University of Alabama and participating institutions manage the data according to Health Insurance Portability and Accountability Act requirements.

Patient population

We examined data from all patients aged 19 years and older who received the SynCardia temporary TAH (TAH-t) 70 mL (SynCardia Systems, LLC, Tucson, AZ; Figure S1, available online at www.jhltonline.org) between June 23, 2006, and April 30, 2017, as a bridge to transplantation or candidacy. This device is the only of its kind approved by the United States Food and Drug Administration.

Analytics

The Data Coordinating Center at the University of Alabama performed the data analysis. Patient condition at implant was categorized according to the INTERMACS Patient Profiles (IPP).[21] For descriptive purposes, categoric variables are expressed as frequencies and percentages. Continuous variables are expressed as means ± standard deviation. Discrete variables were compared using the chi-square test. Continuous variables were compared using the *t*-test or non-parametric Wilcoxon rank sum test, as indicated. AE rates were calculated within 3 months and more than 3 months after implant. Device malfunction AEs were examined by separating the events by thrombosis and device malfunction, whether major or minor. Minor events included events (fault alarms, small air leaks, other) that did not cause the patient to have symptoms. All other events were considered major (driveline disconnection, driver failure).

Survival analyses were performed using Kaplan-Meier depictions and parametric survival analysis. Patients were censored at transplant. The mutually exclusive patient outcomes of death, transplant, or alive on a TAH were analyzed using competing outcomes methods. Risk factors for mortality were examined using multivariable analysis in the hazard function domain. Site TAH volume was investigated as cumulative TAH volume at the time of the patient's implantation and total site TAH volume in the registry. These volume indicators were evaluated as continuous variables and at various cut points (e.g., 5, 10, 15 implants). The volume indicator was selected to provide the best fit in the overall risk model. A p-value of < 0.05 was considered statistically significant. Analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC).

Results

Patient characteristics

Complete follow-up data were available from all 450 patients (87% men) who underwent TAH-t implantation during this period, yielding 197.0 patient-years. Mean follow-up was 5.3 months (median, 3.3 months). Patients were an average age of 50 years (range, 19–72 years), 75% were on inotropes, 80% were IPP 1 or 2, and 20% were supported with extracorporeal membrane oxygenation (ECMO). Dilated cardiomyopathy was the etiology leading to biventricular failure in 50% of the patients. More than 95% of patients were on the active list for a heart transplant or underwent TAH-t as a bridge to candidacy.

Baseline characteristics as predictors of RV failure

Baseline characteristics that describe RV failure at the time of implant were present in 82% of patients, including

include dialysis, ECMO, ventilator support–dependent, severely reduced RV ejection fraction, temporary MCS, or moderate or severe tricuspid valve insufficiency (Supplementary Table S1, online).

Patient's size

Weight, body surface area (BSA), and body mass index were examined as potential risk factors in the multivariable analysis but did not reach statistical significance for entry into the model. The cumulative distribution functions for ranges of weight and BSA are included in Supplementary Figures S2 and S3, online.

Hemolysis

The mean lactose dehydrogenase (LDH) value was 574.2 ± 579.7 U/liter (Supplementary Figure S4, online). However, LDH values were available in INTERMACS for only 33% of patients both before and after implantation. The values from the currently available data show LDH remained stable from before implantation throughout the follow-up period.

Survival

Transplantation was performed in 266 patients, and 162 patients died on support. Survival according to Kaplan-Meier estimates was 53.2% at 1 year and 33.9% at 2 years (Figure 1). Hazard function analysis showed an early rapidly decreasing risk that merged with a constant phase at about 4 months. By competing outcome analysis, the overall rate of transplantation was 53%, mortality was 34%, and 13% were alive on a device by 12 months (Figure 2). Survival outcome was highest for patients with an IPP of 3 (Supplementary Figure S5, online) Table 1.

Causes of death

The most common cause of death was multisystem organ failure (36% of deaths), followed by neurologic injury (18%) and elective withdrawal of support (12%; Table 2). Differences in the distribution of causes of death by era or center volume were not significant.

Risk factors for death

A 2-phase multivariable model was developed to determine pre-implant risks factor for death (Table 3). Older age at implantation and the need for dialysis before implantation were significant risk factors for early mortality. The greatest age effect was among patients younger than 40 years, who had more a favorable survival likelihood compared with other age groups (Figure 3). Patients with a history of pre-implant dialysis had a particularly high (> 50%) 6-month mortality (Supplementary Figure S6, online). High creatinine and low serum albumin were risk factors for late mortality.

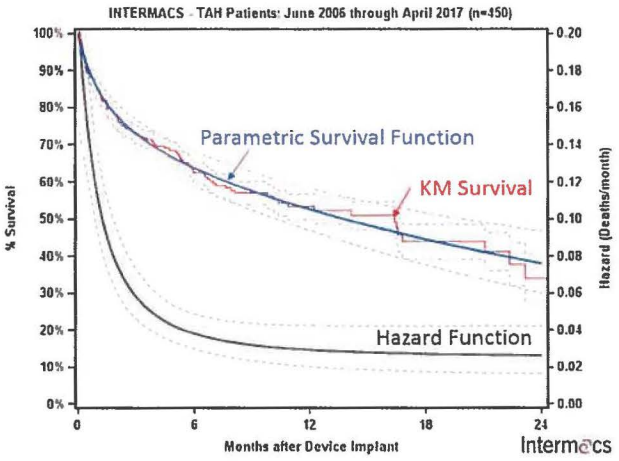

Figure 1 Parametric survival curve and associated hazard function for total artificial heart (TAH) patients. The event modeled is death on a device censored at transplant. The Kaplan-Meier (KM) survival estimates are plotted to show the agreement with the fitted parametric model. The dashed lines indicate the 70% confidence limits. INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support.

The cumulative center TAH-t volume of ≤ 10 implants was a significant risk factor in the constant phase (Figure 4). The cutoff at a center volume of 10 implants was identified as the best descriptor of center volume as a risk factor. The 12-month survival was 64.8% for centers with more than 10 implants vs 36.7% for those with 10 or fewer ($p = 0.001$). The relationship between age and center volume (Figure 5) shows the particularly favorable outcomes in younger patients in centers with more experience.

Adverse events

The most common AEs early (<3 months) were bleeding and infection. After 3 months, minor device malfunction and infection were most prevalent (Table 4). The AE rates for bleeding, infection, and neurologic dysfunction for TAH-t

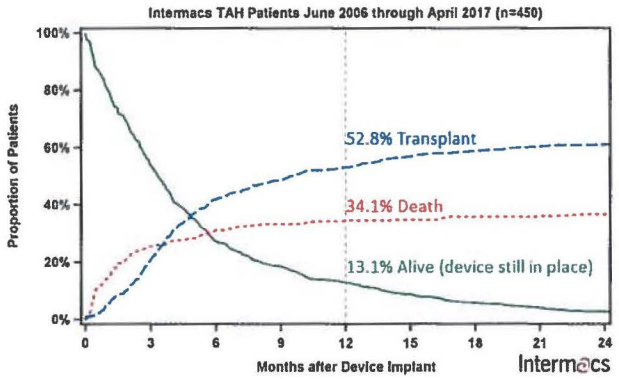

Figure 2 Competing outcomes depiction for patients who received a total artificial heart (TAH) from June 2006 through April 2017 ($n = 450$). At any point in time, the sum of the proportions of each outcome equals 1. INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support.

Table 1 Interagency Registry for Mechanically Assisted Circulatory Support Total Artificial Heart Patients—Characteristics (June 2006 through April 2017)

Characteristics	TAH patients (n = 450)
Age at implant, years	50.1 ± 12.7
Male	393 (87.3)
Weight, kg.	90.5 ± 20.2
Body surface area, m^2	2.1 ± 0.3
Diagnosis	
Congenital heart disease	15 (3.3)
Dilated myopathy	225 (50.0)
Hypertrophic cardiomyopathy	13 (2.9)
Ischemic cardiomyopathy	92 (20.4)
Restrictive cardiomyopathy/other	105 (23.3)
INTERMACS Patient Profile	
1 (critical cardiogenic shock)	189 (43.1)
2 (progressive decline)	163 (37.1)
3 (stable but inotrope dependent)	43 (9.8)
4 (resting symptoms)	32 (7.3)
5-7 (less sick)	12 (2.7)
Device strategy	
Bridge to transplant, listed	267 (59.3)
Bridge to candidacy	169 (37.6)
Destination therapy	7 (1.6)
Rescue therapy, other	7 (1.6)
Hemoglobin, g/dl	10.5 ± 2.1
Creatinine, mg/dl	1.6 ± 1.0
INR, international U	1.4 ± 0.6
Platelets, $\times 10^3/\mu l$	176.5 ± 86.4
Albumin, g/dl	3.3 ± 0.8
Total bilirubin, mg/dl	2.1 ± 3.1
Brain natriuretic peptide, ng/liter	1,338.9 ± 1,164.4
Blood urea nitrogen, mg/dl	32.4 ± 21.7
Alanine aminotransferase, U/liter	126.0 ± 330.4
Aspartate aminotransferase, U/liter	131.7 ± 370.4
Sodium, mEq/liter	134.5 ± 5.9
Cardiac index, liter/min/m^2	2.3 ± 1.4
Pulmonary artery	
Diastolic pressure, mm Hg	25.4 ± 8.7
Systolic pressure, mm Hg	45.3 ± 14.5
Wedge pressure, mm Hg	25.4 ± 8.3
Right atrial pressure, mm Hg	16.6 ± 7.9
Ascites	53 (16.4)
LVEDD, cm	6.3 ± 1.4
LVEF	
<20 (severe)	243 (55.7)
20-29 (moderate/severe)	87 (20.0)
30-39 (moderate)	24 (5.5)
40-49 (mild)	16 (3.7)
>50 (normal)	34 (7.8)
Not recorded or documented/unknown	32 (7.4)
Regurgitation (moderate/severe)	
Mitral	192 (44.0)
Tricuspid	218 (50.0)
Aortic	20 (4.6)
RVEF (severe)	146 (33.5)
ECMO	94 (20.9)

ECMO, extracorporeal membrane oxygenation; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction.
Continuous data are presented as mean ± standard deviation and categoric data as number (%).

Table 2 Interagency Registry for Mechanically Assisted Circulatory Support Total Artificial Heart Patients— Primary Cause of Death (June 2006 through April 2017, n = 450)

Primary cause of death	Patients No. (%)
Multisystem organ failure	59 (36.4)
Neurologic dysfunction	29 (17.9)
Withdrawal of support	19 (11.7)
Major infection	17 (10.5)
Respiratory failure	8 (4.9)
Heart Failure	7 (4.3)
Device malfunction	5 (3.1)
Bleeding	4 (2.3)
Gastrointestinal disorder	3 (1.9)
Hepatic dysfunction	3 (1.9)
Fluid/electrolyte disorder	1 (0.6)
Pulmonary embolism	1 (0.6)
Other	6 (3.7)
Total	162 (100)

were higher in the early phase compared with data from the INTERMACS registry of patients receiving LVADs.

The likelihood of major infection approached 70% within 6 months (Supplementary Figure S7, online). There were 556 infections documented in 450 patients. Pulmonary infections after implantaion were the most common type, with bacteria being the most common pathogen (Supplementary Tables S2 and S3, online).

A total 188 neurologic dysfunction events occurred. The incidence of stroke was 22.7% within the first 6 months: 13.5% ischemic and 10.2% hemorrhagic strokes (Supplementary Figure S8, online). A modified Rankin scale was applied to only 51 events; the scores indicated that 12% of these events resulted in moderate-severe disability and 39% in severe disability.

Approximately 20% of patients experienced a major gastrointestinal hemorrhage within 6 months of implantation (Supplementary Figure S9, online). The incidences of major and minor device malfunction were 7.1% and 28.2% at 6 months, and the incidence of thrombosis was 1.6% during this same interval (Supplementary Figure S10, online).

Table 3 Interagency Registry for Mechanically Assisted Circulatory Support Total Artificial Heart Patients—Multivariable Model (June 2006 through April 2017, n = 450)

Pre-Implant Risk Factor for Death	Early hazard		Constant hazard	
	HR	p-value	HR	p-value
Age, year (older)[a]	1.6	0.001		
Pre-implant dialysis	2.5	0.006		
Creatinine (higher)			1.3	0.008
Albumin, g/dl (lower)[b]			1.9	<0.001
Total center TAH volume ≤10			3.0	<0.001

HR, hazard ratio; TAH, total artificial heart.
[a]The hazard ratio depicts the increase in hazard when age increases from 50 to 60 years
[b]The hazard ratio depicts the increase in hazard when albumin decreases 1 unit.

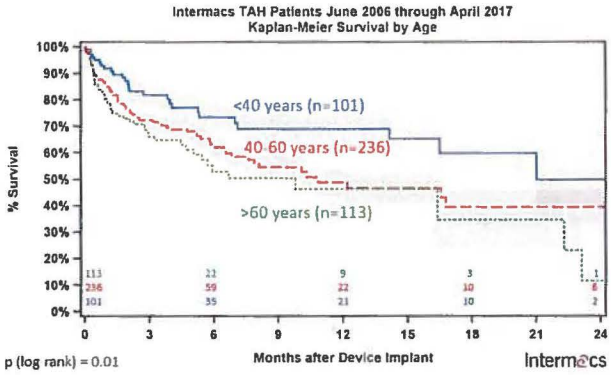

Figure 3 Kaplan-Meier survival curves for total artificial heart (TAH) patients stratified by age. INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support.

Pre-implant dialysis was performed in 51 patients (11%). For the 399 patients who did not require dialysis before implantation, 114 (29%) began dialysis after TAH-t implantation. We were unable to identify the number of patients who were weaned from dialysis. The mean creatinine and serum urea nitrogen values remained stable from baseline to 6 months after implantation (Supplementary Figures S11 and S12, online). To determine a relationship between hemolysis and renal failure dysfunction, LDH levels were analyzedto determine whether hemolysis was a risk factor for dialysis. Pre-implant and post-implant (follow-up) LDH levels were compared in 2 groups: (1) no dialysis before and after implantation and (2) no dialysis before implantation but with the need for dialysis after implantation. The difference in LDH levels for both groups was not statistically significant (Supplementary Figure S13, online). All AE rates for the TAH-t cohort were highest during the first 3 months.

Discharged home and hospitalization

Overall, 109 patients (24%) were discharged with device support: 91% were discharged to a home setting, and 4% were discharged to a rehabilitation unit. Of the 370 patients who received an LVAD after 2010, 99 (27%) were discharged home on the device. The median time from implantation to discharge home for discharged patients was 1.6 months (interquartile range, 1.1–2.3 months). The number of patients discharged increased in the most recent area (Supplementary Tables S4–6, online).

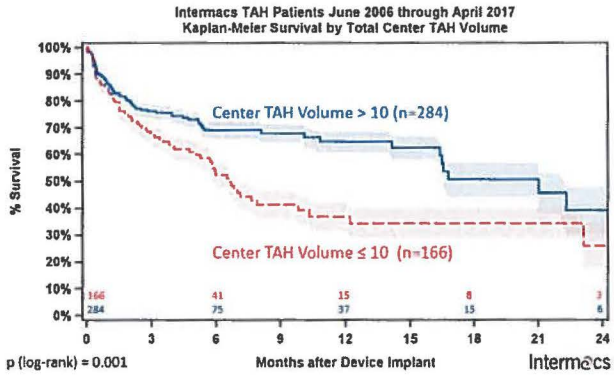

Figure 4 Kaplan-Meier survival curve for total artificial heart (TAH) patients stratified by total center volume. INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support.

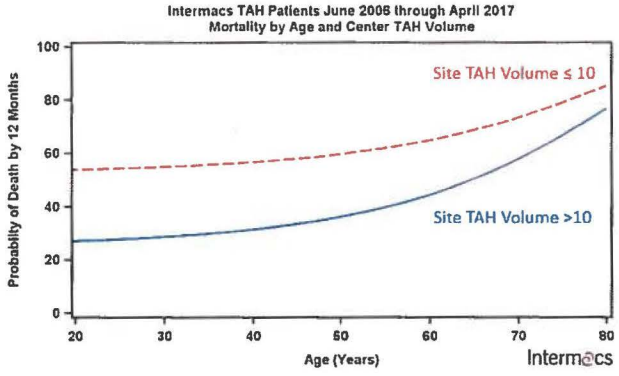

Figure 5 Predicted probability of mortality by 12 months by total center total artificial heart (TAH) volume. Predicted 12-month survival is based on a multivariate parametric hazard model using the average patient characteristics. INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support.

Likelihood of transplantation

The possibility of undergoing heart transplantation differed widely by era and center volume. Among centers implanting more than 10 TAH-t during the study period, 58.4% of patients received a heart transplant within 12 months vs 43% in lower-volume centers (Figure 6). The year of

Table 4 Interagency Registry for Mechanically Assisted Circulatory Support Total Artificial Heart Patients—Adverse Events (June 2006 through April 2017, $n = 450$)

	Early[a]		Late[a]		
Event	Events	Rate[b]	Events	Rate[b]	p-value[c]
Thromboembolism					
Venous	17	1.7	3	0.2	0.0001
Arterial non-CNS	20	2.0	2	0.1	<0.0001
Bleeding	414	41.3	96	7.1	<0.0001
Device malfunction					
Major	13	1.3	34	2.5	0.04
Minor	50	5.0	203	14.9	<0.0001
Pump thrombus	4	0.4	3	0.2	0.4
Hepatic dysfunction	52	5.2	11	0.8	<0.0001
Infection	389	38.8	167	12.3	<0.0001
Neurologic dysfunction	148	14.7	40	2.9	<0.0001
Pericardial drainage	63	6.3	1	0.1	<0.0001
Renal dysfunction	162	16.1	21	1.5	<0.0001
Respiratory failure	219	21.8	38	2.8	<0.0001

CNS, central nervous system.
[a]Early indicates ≤ 3 months of device implant. Late indicates > 3 months after device implant
[b]Rates are reported per 100 patient-months.
[c]The *p*-values compare early and late rates.

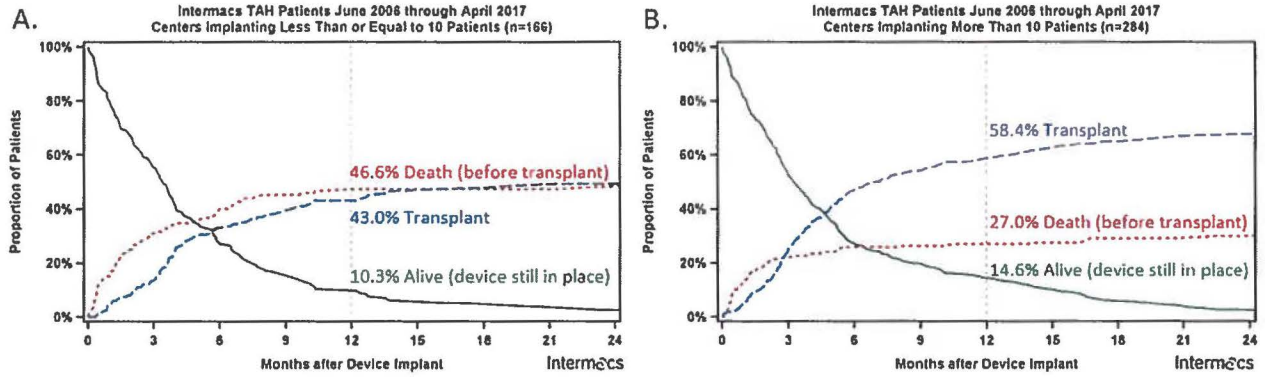

Figure 6 Competing outcomes for centers implanting (A) ≤ 10 patients ($n = 166$) and (B) > 10 patients ($n = 284$). At any point in time, the sum of the proportions of each outcome equals 1. INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; TAH, total artificial heart.

implantation also had an effect on the chances of transplantation (Figure 7), with a higher likelihood of transplant within 1 year for implants taking place before 2012.

Discussion

Several publications during the last few decades have shown a wide range of outcomes in patients undergoing TAH implantation.[22–32] This analysis of initial data from the INTERMACS database represents a comprehensive multi-institutional investigation of the TAH-t experience, providing outcomes, risk factors for death, and AE rates to establish benchmarks. Future analyses of the INTERMACS database will provide in-depth understanding of patients' renal function before and after implantation, rates of hemolysis and neurologic events, quality of life, hospitalization and functional capacity, and their care after hospitalization.

Outcomes data for TAH-t obtained from INTERMACS are typically reported annually, with the most recent being in 2015 and 2017;[33,34] the results of the first analysis of data from the Pediatric Interagency Registry for Mechanical Circulatory Support database (the pediatric-specific portion of INTERMACS) were published in 2016.[35] The current analysis of the INTERMACS database shows that the patient cohort that received TAHs-t was sicker (IPP 1 and 2) than patients who received LVADs (more frequently IPP 2 and 3). One or more characteristics of RV failure were present in 82% of patients implanted with a TAH-t.

These characteristics are not surprising, because severe biventricular failure is the indication for the TAH-t. However, each center that implants the TAH-t has developed different criteria to select the appropriate patient with biventricular failure, ranging from determining RV functional parameters calculated preoperatively, etiology of biventricular failure (potential for RV function reversibility) to perioperative hemodynamic assessment with intraoperative visual inspection of RV contractility.

Although the overall 6-month survival for the TAH-t cohort is lower than that of patients who received an isolated LVAD, these patient sub-sets are not comparable in that the TAH-t was selected because LVAD support was deemed inappropriate secondary to biventricular failure.[36,37] Initial consideration was given to comparing the TAH-t cohort to patients in INTERMACS who had received BiVAD support, but this proved to be a challenge. Patients who have received BiVAD in the INTERMACS database were implanted with permutations of different LVADs and RVADs. Furthermore, the outcomes of some of the

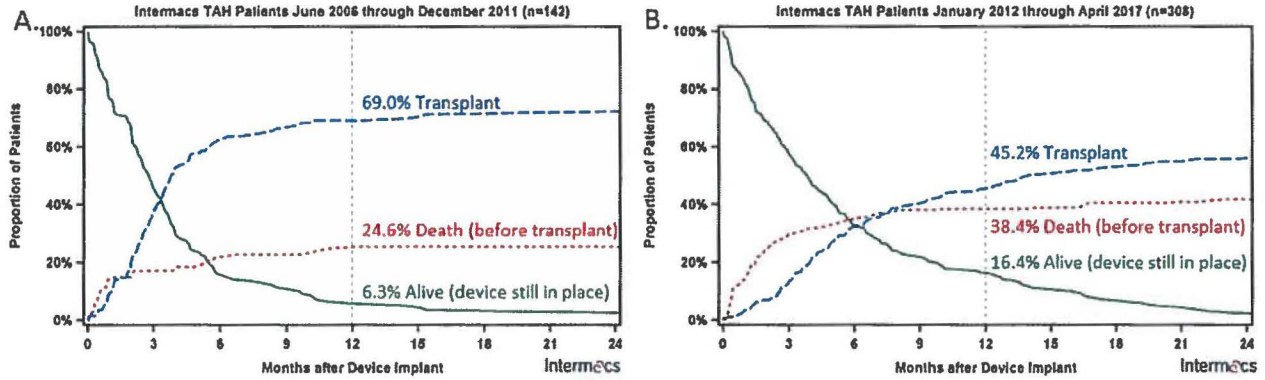

Figure 7 Competing outcomes by implant era: (A) June 2006 through December 2011 ($n = 142$) and (B) January 2012 through April 2017 ($n = 308$). At any point in time, the sum of the proportions of each outcome equals 1. INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; TAH, total artificial heart.

BiVAD configurations have been studied (retrospectively, prospectively, or randomized). Some configurations use different energy sources or are implanted off-label.

The major period of risk for mortality with the TAH-t was the first 3 months. Further analysis showed that center experience with the TAH-t (particularly with >10 implants) is an essential determinant of success, with no discernible difference in the level of patient sickness at the time of implantation. The observed decrease in survival between eras can be attributed to an increase in newer programs performing a small number of implants. The Kaplan-Meier survival estimate by center volume shows a survival advantage when the center volume exceeds 10 devices implanted, a value that differentiates the high-volume from the low-volume centers at 3 months and beyond (i.e., the constant phase).

The mortality in the early phase, which is similar at both high-volume and low-volume centers, is the result of the severity of the patient's condition. The mortality in the constant phase is primarily the result of medical issues (i.e., elevated creatinine and low albumin concentrations) and management (experience). This finding suggests that not only the severity of the patient's illness but also the level of experience of the team managing the patient is important. The improvement in TAH survival could be the result of surgical experience with device implantation, a better understanding of patient selection, the timing of intervention, and patient management. The survival from the high-volume centers at 1 year is approximately 66%, and destination therapy LVAD survival at 1 year is 78%. Although these survival outcomes are dissimilar, they are within range of one another. The improvement in medical management because of more experience argues in favor performing destination therapy in patients with TAHs in high-volume centers. The outcome gap that exists between low-volume and high-volume centers must improve to provide overall better outcomes.

The device malfunction rate was high in the period of 3 to 24 months because of frequent changes that the Freedom Driver required, not because of pump-component failure or thrombosis. The higher AE rates in the early phase after the implantation of TAH-t vs LVAD were multifactorial and might represent the patient severity of illness, coagulation state, and center experience. AEs decrease over time as the patient moves away from the pre-implant physiologic state and the surgical intervention. Pericardial drainage decreased as the risk of mediastinal bleeding decreased over time.

This retrospective analysis indicated that the primary application of the TAH-t has been in the very ill patient with biventricular failure. According to the data from INTERMACS, principal pre-implant diagnoses have been dilated and ischemic cardiomyopathies. During the past few years, those diagnoses have changed to include failing heart transplant (acute or chronic), restrictive and infiltrative cardiomyopathy, congenital abnormalities, malignant arrhythmias that do not respond to other interventions, large post-infarction ventricular septal defects, partial ventricular thrombosis, cardiac malignancies, and Chagas disease. Rebridging with a TAH-t has been successful in some patients who experience LVAD/BiVAD failure.[38]

The challenges for early MCS referral continue to be multifactorial. The timing of referral and intervention might make the difference for some etiologies between successful implant of an LVAD and irreversible RV dysfunction requiring a TAH-t. Nonetheless, as LVADs continue to improve and become ubiquitous, there remains a group of patients whose diagnoses appear best treated with heart replacement. The TAH-t allows for home discharge and outpatient follow-up while the patient awaits transplantation.[39]

The benefits of LVADs in providing significant survival and quality of life benefit for those patients with progressive hemodynamic deterioration are well summarized.[40] The increase in mortality with patients in cardiogenic shock (IPP 1) has led to a decrease in the proportion of such patients receiving LVAD devices. The recent increase in the use of short-term MCS has proven to be encouraging for the severely ill patient in cardiogenic shock as a bridge to decision and durable LVAD. However, this use is associated with an increase in early mortality, partly because of unrecognized RV failure.[41] The encouraging survival in this patient sub-set with the TAH-t, particularly with sufficient center experience, provides support for consideration of the TAH as an alternative to the use of right-sided or left-sided VADs in patients with severe biventricular failure.[42] Pre-implant dialysis is a risk factor for death but is not a contraindication for the use of TAH-t. Successful bridging to heart-kidney transplantation has been performed.[43] A small number of patients are still alive 5 years after implantation of their original TAH-t, leading to the development of an ongoing destination therapy trial of TAH in the United States and Europe.

The concept of TAH continues to evolve as more efficient drivers are developed for the SynCardia TAH-t. The CARMAT TAH has started a trial in Europe.[44] The BiVACOR TAH is a design using magnetic levitation technology that can generate continuous or pulsatile flow.[45] The quest for a long-term heart replacement continues with designs in the form of the ReinHeart TAH,[46] CCFTAH,[47] OregonHeart TAH,[48] Helical Flow TAH,[49] and a hybrid CF-TAH.[50] The concept of a bioartificial TAH has also been proposed.[51]

The patients who benefit from the TAH are among the sickest patients we encounter. Regardless of whether we accept the current technology, the present-day TAH has taught us how to select and manage patients with complex cardiac conditions. This knowledge will serve as the foundation for the future management of patients with the TAH and technologies to come. The concept of heart replacement continues to have value in patients with otherwise fatal biventricular failure.

This study has some limitations. Including the significant amount of data available in the INTERMACS database is not possible in a single report. Some areas that need further analysis include transplant survival after TAH bridge, need for heart-kidney transplant, quality of life, and more data regarding modified Rankin Scale scores for those patients

with neurologic events. Further analysis of the INTERMACS database will be performed to address these relevant issues.

Disclosure statement

F.A.A. and V.K. are consultants and trainers for SynCardia Systems. I.G. and F.E. are principal investigators in SynCardia Systems clinical trials. R.G.S. is a consultant for SynCardia Systems. None of the other authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

The authors thank Cara Cruz for her technical and organizational support.

Appendix A. Supporting information

Supplementary data are available in the online version of this article at www.jhltonline.org.

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TAB 2

SynCardia Systems, LLC
1992 E. Silverlake Rd.
Tucson, Arizona 85713
Phone: 520.545.1234
Fax: 520.903.1782

ETIOLOGIES

(As of 4/5/19)

ETIOLOGIES	Total # of Cases (70cc & 100cc)
Ischemic Cardiomyopathy	594
Dilated Cardiomyopathy	597
Failure to Wean	195
Other Conditions	162
Non-Ischemic Cardiomyopathy	166
Congenital & Genetic Conditions	142
Post HTX Graft Failure	104
Valvular Cardiomyopathy	84
LVAD Failure	79
Restrictive Cardiomyopathy	69
Viral Cardiomyopathy	39
Post/Peripartum Cardiomyopathy	19
Infectious Complications	13

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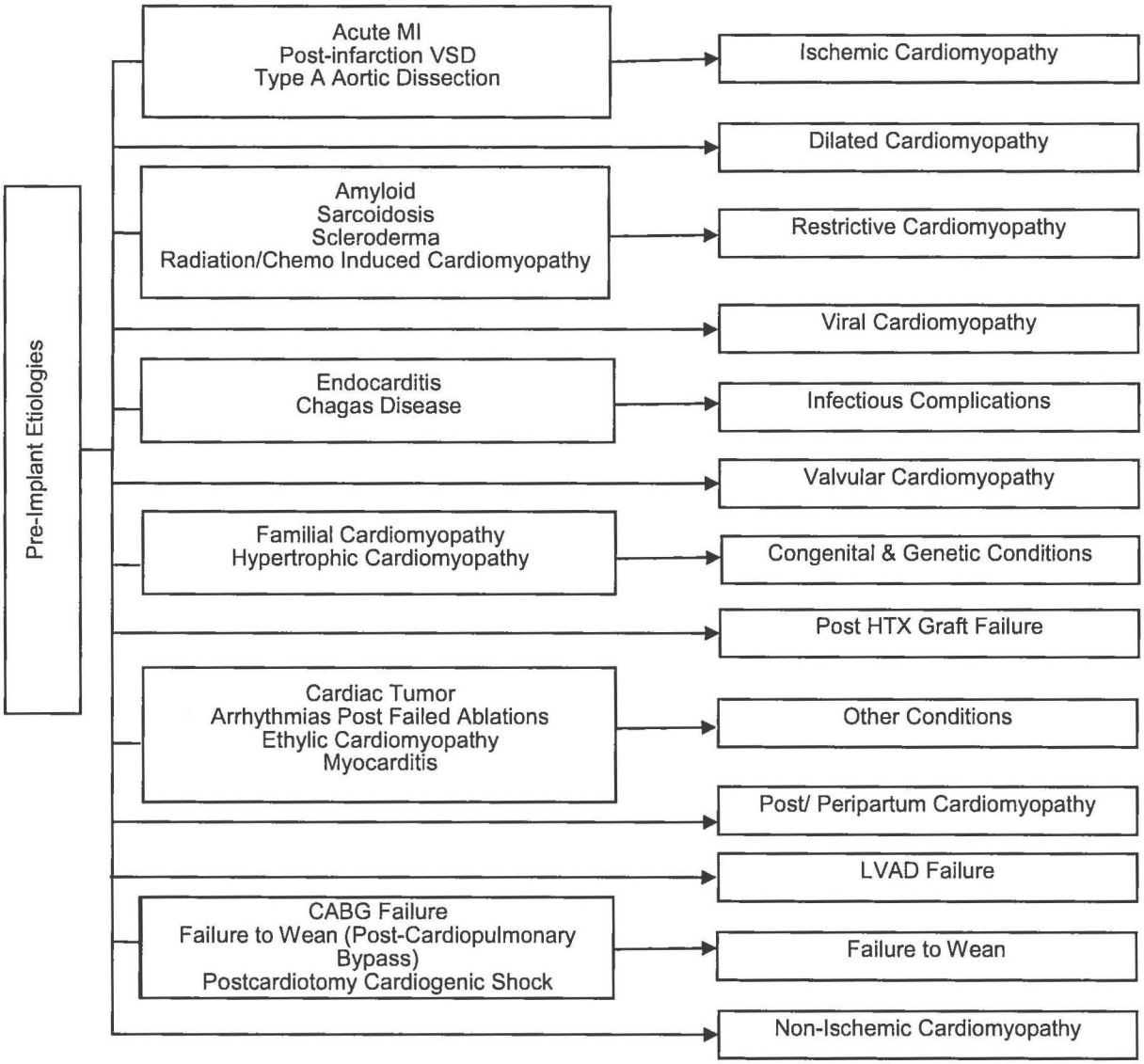
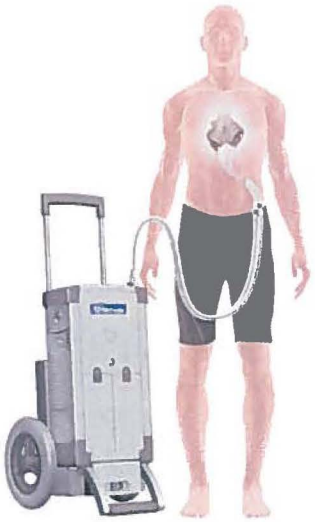
The etiologies above are grouped as follows:



TAB 3

SynCardia Systems, LLC
70cc temporary Total Artificial Heart (TAH-t)

Instructions for Use with the Companion 2 Driver System



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CAUTION: In the United States, the use of the SynCardia 70cc TAH-t for destination therapy is investigational.

CAUTION: In the United States, the use of the Companion 2 Driver System with the 70cc TAH-t for the destination therapy indication is investigational.

CAUTION: Federal (USA) law restricts this device to sale by or on order of a physician.

EC	REP

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2514 AP The Hague
The Netherlands

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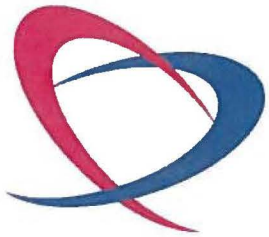
16 MAY 2005

900301-002 / C2-900001 Rev 013
Revision Date: 2018-01



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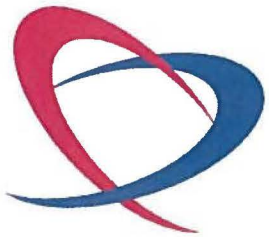


Chapter 1. Device Description

The SynCardia TAH-t Companion 2 Driver System (TAH-t System) (**Figure 1-1**) is comprised of the SynCardia temporary Total Artificial Heart (TAH-t) and the Companion 2 Driver and includes a Hospital Cart and Caddy.

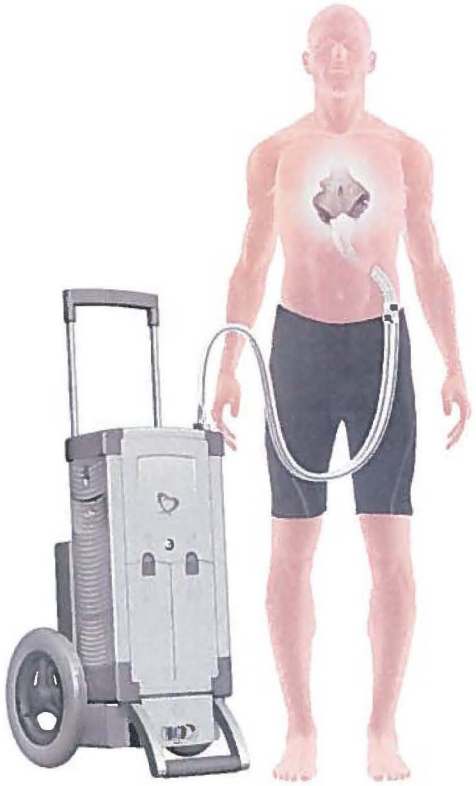


Figure 1-1 – TAH-t System

The SynCardia temporary Total Artificial Heart (TAH-t) (**Figure 1-2**) is an implantable pulsatile biventricular device that replaces a patient's native ventricles and valves and pumps blood to both the pulmonary and systemic circulation.

Figure 1-2 –TAH-t

The Companion 2 Driver System (**Figure 1-3**) is a multi-component electro-mechanical unit designed to provide pneumatic power to the implanted TAH-t. The Companion 2 Driver System includes a Driver, a Hospital Cart, and a Caddy.

Figure 1-3 – Companion 2 Driver System Major Components

1.1 The Implantable TAH-t

The implantable TAH-t consists of two artificial ventricles, each made of a semi-rigid polyurethane housing with four flexible polyurethane diaphragms separating the blood chamber from the air chamber. The diaphragms allow the artificial ventricle to fill and then eject blood when compressed by air from the external driver. Valves, mounted in the inflow and outflow ports of each artificial ventricle, control the direction of blood flow. The maximum dynamic stroke volume of each ventricle allows for generating a flow rate up to 9.5 liters per minute.

The left artificial ventricle is connected via the left atrial inflow connector to the left atrium, and via the aortic outflow connector to the aorta. The right artificial ventricle is connected via the right atrial inflow connector to the right atrium and via the pulmonary artery outflow connector to the pulmonary artery. The cannula from each artificial ventricle driveline is tunneled through the chest wall. The cannulae of the right and left artificial ventricles are attached to seven-foot pneumatic drivelines that connect to the driver.

1.2 TAH-t Theory of Operation

Blood enters the TAH-t through the patient's native atria, passing through an inflow cuff that has been anastomosed to the atrium at the level of the atrioventricular valve annulus. The cuff attaches to the rigid housing of the TAH-t via an inflow valve that allows blood to enter the polyurethane ventricle.

Pulses of air generated by an external driver and delivered by a driveline distend the ventricle diaphragm and expel blood from the ventricle through an outflow valve into an outflow graft anastomosed to the aorta or pulmonary artery. The TAH-t will fully support the patient's circulation.

The basic concept for utilizing the TAH-t is "partial fill, full eject." A graphic representation of a typical pressure curve for the pulse of air delivered to the TAH-t ventricle is shown in **Figure 1-4** below.

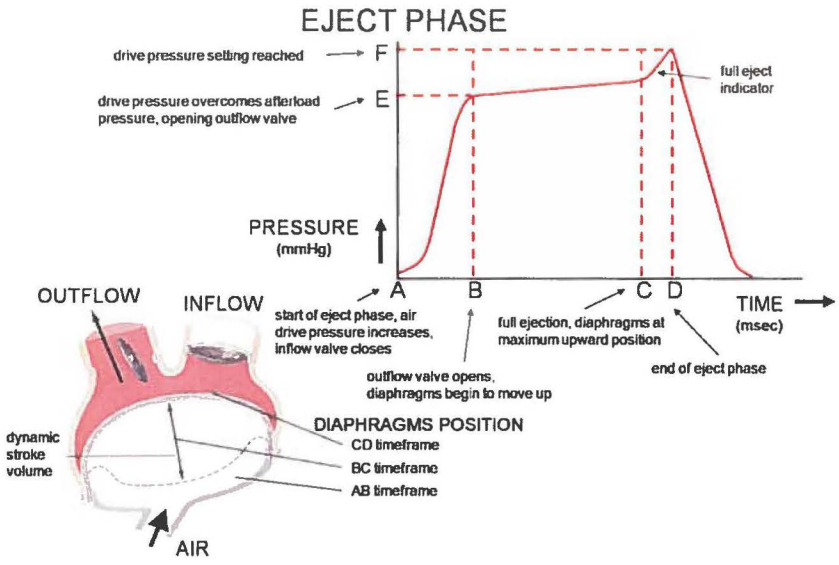


Figure 1-4 – Typical Pressure Waveform for the TAH-t

The pressure waveform contains features that are indicative of the implanted TAH-t performance during systole. The initial segment of the pressure waveform (A to B) communicates a quick rise in pressure as the air side of the ventricle is pressurized until the drive pressure overcomes the afterload pressure and the outflow valve is opened.

During the period between B and C, air continues to enter the air chamber of the ventricle as the diaphragm moves to eject blood, resulting in a sharply reduced rate of pressurization when compared to the front edge.

When the diaphragm is unable to move further, the pressure increases as air continues to enter the isovolumetric air chamber of the ventricle, resulting in a display of a "full eject" flag, indicated by the region from C to D. The Driver then begins diastole, pressure in the air chamber is vented, and the waveform moves towards the starting pressure line on the X-axis.

Reduction of the systolic drive pressure results in reduced cardiac output and increased venous pressures, as the pressure produced by the driver does not exceed the afterload pressure of the patient. Full ejection increases organ perfusion and diminishes blood stasis. Full ejection of the left ventricle is generally achieved by providing a drive pressure that is 30 – 40 mmHg higher than the aortic pressure.

The "partial fill" portion of the operating concept is derived from the Frank-Starling mechanism, which states that the heart has the intrinsic capability of increasing its force of contraction, and therefore its stroke volume, in response to an increase in venous return. The Frank-Starling principle is based on the length-tension relationship within the ventricle. If ventricular end diastolic volume (preload) is increased, it follows that ventricular fiber length is also increased, resulting in an increased 'tension' of the muscle.

In this way, cardiac output is directly related to venous return, the most important determining factor of preload.

When the heart rate is constant, cardiac output is directly related to preload, up to a certain point. An increase in preload will increase the cardiac output until very high end diastolic volumes are reached. At this point cardiac output will not increase with any further increase in preload, and may even decrease after a certain preload is reached.

In the TAH-t, the Starling mechanism is implemented by balancing three other parameters: heart rate, percent systole, and vacuum. By reserving a space within the ventricle that is not used when the patient is at rest, the venous return may increase, which results in a higher stroke volume. As long as volume overload is avoided, the TAH-t can behave along a Starling curve with venous return translated into increased cardiac output.

The fill volumes are established using the flow waveform generated during diastole, as depicted in **Figure 1-5**. The initial part of the curve, (A to B) is characterized by a rapid movement of air as the pressure in the air chamber of the TAH-t is relieved and the outflow valve closes. The inflow valve opens at point B and blood enters the blood chamber of the ventricle, while air is exhausted from the ventricle.

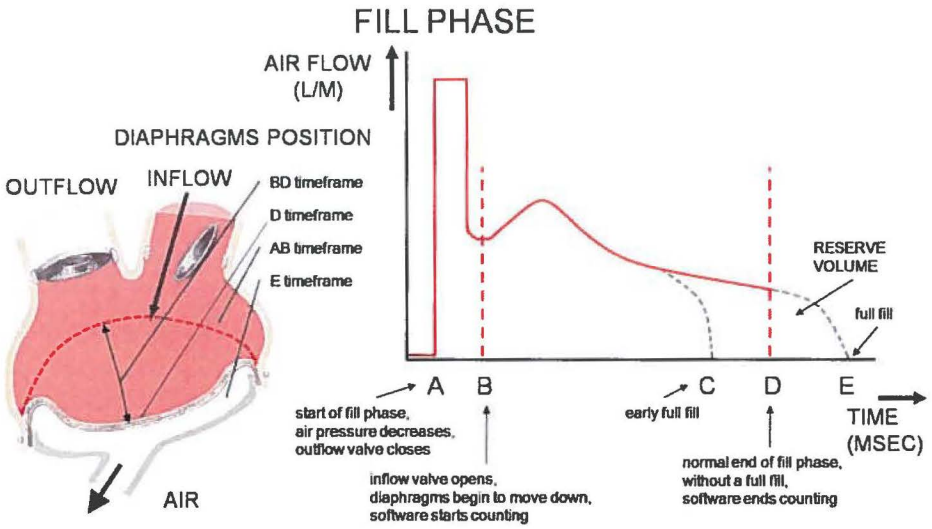


Figure 1-5 – Typical Flow Waveform for the TAH-t

The duration of the period indicated from B to C, D or E, prior to initiation of systole, is indicative of whether the device is partial or full filling the ventricle. It is this region that is measured to determine the fill volume of the ventricle. Integrating the area under the flow curve once the inflow valve has opened provides the stroke volume of the ventricle, provided that full ejection has occurred. The fill volume multiplied by the heart rate provides the device cardiac output.

Full filling of the ventricle is represented by an abrupt mid-diastolic drop of flow rate to zero, as indicated by point C. Increasing the heart rate will increase the cardiac output, but will also decrease the blood fill volume by decreasing the amount of time allowed for filling the ventricle. Adjustment of the percent systole control will vary the time of the cardiac cycle that the device remains in systole. Modification of the percent systole can be used to optimize the filling time of the ventricle. The vacuum control provides another means to control ventricular filling such that increasing the negative diastolic pressure will result in increased ventricular filling.

1.3 The Companion 2 Driver System

The Companion 2 Driver System operates and monitors the TAH-t throughout the TAH-t implantation, surgical recovery phase in the ICU and step-down units and also the ambulatory phases of patient support. The Companion 2 Driver System includes a Driver, a Hospital Cart and a Caddy.

- The Driver powers the TAH-t and docks into the Hospital Cart or Caddy. Data from the TAH-t and the patient are monitored non-invasively by the Driver so there are no electrical connections to the patient.
- The Hospital Cart is a large cart with wheels, into which the Driver docks. It is intended for use in the hospital during the TAH-t implant procedure and subsequent surgical recovery phase.
- The Driver System Caddy is a small cart with wheels into which the Driver docks for use inside the hospital. It is designed to facilitate mobility of ambulatory patients within the hospital.

See the *SynCardia Companion 2 Driver System Operator Manual* for detailed information on the Companion 2 Driver System.

1.4 The Discharge Driver

The Freedom Driver System is a portable multi-component electro-mechanical unit designed to provide pneumatic power to the implanted SynCardia TAH-t to support clinically stable TAH-t patients in and out of the hospital. The Freedom Driver provides the same pumping ability as the CSS Console or Companion 2 Driver System for clinically stable TAH-t patients while being significantly smaller in size.

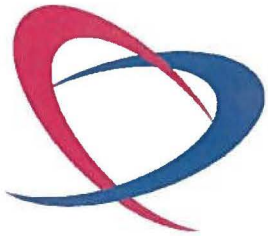
See the *SynCardia Freedom Driver System Operator Manual* for detailed information on the Freedom Driver System.

Chapter 2. Indications for Use

2.1 The 70cc TAH-t System is indicated for use as a bridge to transplantation in cardiac transplant-eligible candidates at risk of imminent death from biventricular failure.

2.2 The 70cc TAH-t System with the Companion 2 Driver is intended for use inside the hospital and on the hospital grounds, during and after surgical implantation of the TAH-t.

2.3 The use of the SynCardia 70cc TAH-t for destination therapy (for patients who are ineligible for cardiac transplantation and for whom clinical indices indicate a remote likelihood of becoming eligible for a transplant) is investigational.



Chapter 3. Contraindications

The TAH-t System is contraindicated for use in:

- Patients who do not have sufficient space in the chest area vacated by the natural ventricles. Generally this includes patients who have body surface areas <1.7m², or who have a distance between the sternum and the 10th anterior vertebral body measured by computed tomography imaging (CT scan) < 10 cm.
- Patients who cannot be adequately anticoagulated on the TAH-t.

Chapter 4. Warnings

4.1 Setup and operation of the TAH-t System should only be performed by personnel trained and certified in accordance with the SynCardia training program. A thorough understanding of the technical principles, clinical applications, and risks associated with the device is necessary. Prior to use, refer to the *SynCardia Companion 2 Driver System Operator Manual.*

4.2 Sterile components of the TAH-t are intended for single use only. Do not use if the package is opened or damaged. Do not re-sterilize or reuse.

4.3 Safe use of the TAH-t System has not been established in pregnant patients.

4.4 Do not subject patients implanted with the TAH-t to magnetic resonance imaging (MRI) scans.

4.5 Do not use the TAH-t System if the implantable artificial ventricles cannot fit in the chest area vacated by the natural ventricles. Compression of the inferior vena cava and left pulmonary vein are possible consequences.

4.6 Do not allow any catheter to get near the inflow valves of the TAH-t. If a catheter migrates into an inflow valve, the valve could become stuck, limiting flow. Confirm the position of the catheter by x-ray after catheter insertion and repeat an x-ray immediately if any unexplained sudden drop in cardiac output occurs. A percutaneously inserted central catheter may migrate into the inflow valve when the patient raises his or her arm.

4.7 There is a potential for air embolism. De-air the artificial ventricles to minimize the possibility of air inadvertently entering the device.

4.8 Do not allow the external drivelines to become kinked. If there is any low cardiac output alarm, inspect the external drivelines for kinking.

4.9 A reduction in the maximum stroke volume on the external driver monitoring computer to below 50 milliliters may indicate a failure of one of the diaphragms in a ventricle of the TAH-t.

4.10 Do not administer CPR to TAH-t patients. Defibrillation and CPR are ineffective on patients implanted with the TAH-t.

Chapter 5. Precautions

5.1 Surgical, nursing, and perfusion staff responsible for the SynCardia TAH-t program at each hospital must complete the SynCardia TAH-t Training program.

5.2 The SynCardia TAH-t and Drivelines are provided sterile; caution must be taken in opening the package. Do NOT resterilize. Do NOT use if package is damaged. Storage temperature for the drivelines is 10 - 50°C.

5.3 Measures should be taken to prevent infection or sepsis. Use strict aseptic techniques during implantation.

5.4 The outflow grafts must be pre-clotted before use.

5.5 Do not use an antifibrinolitic agent like Amicar with an active clotting agent like FEIBA.

5.6 Use only water-soluble antiseptic cleaners around the exit site. Ointments may delay tissue in-growth around the driveline cannulae.

5.7 Each Driver contains two independent compressor subassemblies, each capable of providing independent support for operation of the TAH-t. Hospitals and patients supported with the Driver must have an additional Driver available as a backup to be used in the event of a failure of the primary Driver.

Personnel should be trained how to exchange the primary Driver with a backup Driver in the event of system failure. The backup Driver should be connected as quickly as possible. This procedure is for emergency use only. See *SynCardia Companion 2 Driver System Operator Manual*, Chapter 17, *Switching to Companion 2 Backup Driver*.

5.8 The TAH-t System contains ferro-magnetic metal components. Do NOT perform MRI imaging procedures on patients implanted with the TAH-t.

5.9 Manage the exit site in accordance with hospital procedures

5.10 The Cannulae and Drivelines must be inspected daily to make sure they are intact and have no holes. If a hole is detected in the Cannulae or Driveline the hospital should apply a self-fusing silicone tape to seal the hole. The hospital must contact SynCardia for possible further instructions.

5.11 Monitor cardiac output when closing the chest. A reduction in TAH-t output while closing the chest may indicate inflow obstruction. Reposition the TAH-t ventricles by anchoring to a rib or moving it into the left pleural space.

5.12 A sudden reduction in TAH-t flow may be caused by a kink in the pneumatic drivelines, or some inflow obstruction to the TAH-t, such as tamponade. Check and correct any kink in the drivelines.

5.13 Do not administer CPR to TAH-t patients. Defibrillation or CPR will not be effective.

5.14 Flows should be kept at a reasonable output so that proper washing of the ventricles is established.

5.15 The level of anticoagulation will vary depending on the patient's coagulation status. Typically, patients supported with the TAH-t require systemic antithrombotics similar to those used for patients with mechanical valves.

Chapter 6. Summary of Studies

6.1 TAH-t with CSS Console

The multi-center (5) clinical study was conducted of the TAH-t with a large external driver, the Circulatory Support System (CSS) Console. The purpose of the study was to evaluate the device combination as a bridge to cardiac transplantation in transplant-eligible patients at risk of imminent death from biventricular failure.

Ninety-five patients (ages 16-67) were implanted with the TAH-t; 81 (70 males, 11 females) met all inclusion/exclusion criteria and were designated the core implant group. All patients were in NYHA Class IV at time of enrollment. Additional characteristics of the core implant group at the time of entry into the study are:

- 15 patients were on heart-lung machine/ECMO support,
- 51 patients had central venous pressure > 18 mmHg,
- 11 patients had right ventricular ejection fraction < 20%, and
- all patients had relative or absolute contraindications to VAD support, as evidenced by refractory arrhythmias or unresuscitatable cardiac arrest (25), hypokinetic right/left/global ventricles (23), aortic regurgitation, stenosis or prosthesis (13), massive myocardial infarction or direct myocardial injury that affects technical insertion of a VAD through the left ventricle (10), failure to wean from cardiopulmonary bypass with biventricular injury (4), left, right ventricular or mural thrombus (3) or septal defect (3).

All patients were on maximal medical therapy and at imminent risk of death before a donor heart could be obtained.

6.1.1 Trial Success

Treatment success was defined as patients who, at 30 days post transplant, were: 1) alive; 2) NYHA Class I or II, 3) ambulatory; 4) not ventilator dependent; and 5) not on dialysis.

Trial success was achieved in 56 (69%) of the 81 core patients. Sixty-four of the 81 core patients (79%) reached transplant after a mean time of 79 days (range 1-414). Fifty-eight (72%) survived to 30 days post transplant.

6.1.2 Hemodynamics

The hemodynamic performance of the TAH-t was assessed through a comparison of pre- and post-implant values of cardiac index, systolic arterial blood pressure, and central venous pressure. Hemodynamic indices were effectively restored to near normal values. Average cardiac index increased from 1.9 to 3.0 L/min/m^2, average systolic blood pressure increased from 93mmHg to

120mmHg, and average CVP decreased from 20mmHg to 14mmHg.

The average perfusion pressure (mean aortic pressure minus CVP) increased from 49mmHg to 63mmHg, which was associated with recovery of renal and hepatic function.

6.1.3 Adverse Events

Adverse events collected for all 81 core patients while on the TAH-t System are presented in descending order in **Table 6-1**. The adverse events represent 17.6 device years of experience for an overall event rate of 1.9 events per month while on the device awaiting transplant.

Table 6-1
Incidence of Adverse Events in Core Patients
During Device Implantation
in Decreasing Order of Frequency
(Represents 17.6 years or 6411 days on the device)

Adverse Event	Number of Events	Number (%) of Patients n=81
Any Adverse Event	400	76 (93.8%)
Infection	125	58 (71.6%)
Bleeding	55	34 (42.0%)
Respiratory Dysfunction	44	24 (29.6%)
Hepatic Dysfunction	30	29 (35.8%)
Neurological Event	26	20 (24.7%)
Renal Dysfunction	23	21 (25.9%)
Reoperation	18	17 (21.0%)
Device Malfunction	18	15 (18.5%)
Peripheral Thromboembolism	14	9 (11.1%)
Reduced Blood Pressure	13	12 (14.8%)
Reduced Cardiac Index	11	7 (8.6%)
Technical/Procedural	11	3 (3.7%)
Fit Complication	5	5 (6.2%)
Hemolysis	3	3 (3.7%)
Miscellaneous	3	3 (3.7%)

6.2 TAH-t Reliability

Reliability testing was conducted to determine with reasonable assurance how long a device would perform as intended, without failure.

Three separate sets of *in vitro* reliability testing were conducted. In one test, four TAH-t units were run for a period of 180 days. During this time, there were no failures or abnormalities observed.

In a second *in vitro* reliability trial, four TAH-t units were tested in a "run to failure" study design. After 35 months of testing, there were no failures or abnormalities observed.

A third test was initiated using three TAH-t units which had exceeded their three-year sterilization expiration date. This provided information about the effects of long-term storage on the fatigue resistance properties of the TAH-t. After 24 months of testing, there were no failures or abnormalities observed.

In conclusion, a total of 11 units were run for various lengths of time over six years with no device-related failures. The cumulative number of days used for calculation was 6715, and there were no failures or signs of appreciable wear observed. When the 11 units are used to calculate reliability with a 90% confidence, the reliability at 30, 60 and 365 days is as reported in the **Table 6-2**.

Table 6-2
Reliability Test Results with 90% Confidence

# days run	MTBF	Reliability in number of days run		
		30	60	365
6715	2916	0.99	0.98	0.88

Chapter 7. Implant Procedures

Patients are prepared for the implant pursuant to standard hospital procedures for any cardiac surgery. An arterial line, a central line, and standard artificial ventilation are required prior to the start of surgery. Transesophageal echocardiography is recommended.

7.1 Materials Needed but not Provided

The following materials are needed for the surgery but are not provided by SynCardia. They are typically ordered and maintained by the implanting hospital.

- *Three 15 by 20 centimeter sheets of membrane (e.g., Gore-Tex®)* are used to create a neo-pericardium to prevent adhesions.
- *Teflon felt buttress strips* are cut to approximately 10-12 mm in width and are generally 10 cm in length. It usually takes at least two of these to extend around the entire atrial cuff. (See **Section 7.3**, ***Removal of Native Ventricles***)
- *Surgical sealant* is used to coat the outflow grafts.

7.2 Preparation

7.2.1 Pass each sterile TAH-t component onto the sterile field by opening the non-sterile outer bag and dropping or passing the sterile inner bag using sterile technique.

7.2.2 After a standard median sternotomy is performed and before starting heparin,

(1) Prepare the arterial outflow connectors,

(2) Trim atrial inflow connectors to appropriate size, and

(3) Tunnel the artificial ventricle conduits through the skin.

7.2.3 Apply surgical sealant to the two arterial outflow connectors. This is done before cannulation so that there is plenty of time for the outflow connectors to dry before use.

7.2.4 Trim the two inflow connectors. Cut the edges of the atrial quick connects for the atrial anastomoses to a radius extending out from the connector for 5-7 mm. Cut in a completely circular fashion. Then stretch and invert them.

7.2.5 Pass the cannulae through their subcutaneous pathways before heparinization of the patient. Position the left ventricle cannula in the epigastrium at the level of the midclavicular line and approximately 2 inches below the costal margin. Make a semicircular skin flap incision on the left midclavicular line approximately 5 to 10 cm below the costal margin.

7.2.6 Place a long clamp through the subcutaneous tissue, rectus fascia, rectus muscle, and into the chest as a chest tube would be placed.

Use a similar approach to place the cannula for the prosthetic right ventricle, approximately 4 to 5 cm medial to the left ventricle cannula so that no necrosis between the two exit sites will result.

7.2.7 Enlarge the pathway by opening the clamp and inserting a one-inch Penrose drain through the pathway. Place the end of the cannula in the Penrose drain and advance approximately 8-10 cm. Pull the Penrose drains through the pathway that delivers the cannula. Position the artificial ventricles laterally to the wound and cover with a towel while the rest of the procedure takes place. This provides ample opportunity for small bleeders in the cannula pathway to clot.

7.3 Removal of the Native Ventricles

7.3.1 Cannulation of the aorta and both superior and inferior venae cavae is done in a standard fashion. Umbilical tape chokers are used on the cavae. Dissection around the aorta and pulmonary artery is limited to the proximal portion of the aorta in anticipation of transplantation, thus leaving some untouched areas that will not be very fibrotic. Cardiopulmonary bypass is instituted and the heart is fibrillated. Total bypass is instituted by pulling on the choker tapes.

7.3.2 The heart is fibrillated and excision of the ventricles is begun. The excision is different from that used for transplantation. It seeks to preserve the annulus of both the tricuspid and mitral valves. Thus, an incision is made on the ventricular side of the AV groove of the right ventricle (**Figure 7-1**).

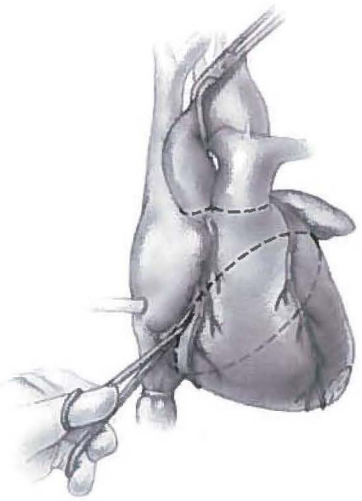


Figure 7-1 – First Incision of Ventricle Excision

7.3.3 Incision can be done with a knife and extended with a knife or scissors. It is extended anteriorly across the right ventricular outflow tract and just proximally to the pulmonary valve. Posteriorly, it is extended to the interventricular septum and across the septum, staying on the left side of the arterioventricular (AV) groove and preserving the entirety of the mitral annulus. The

anterior and posterior lines of incision are dissected apart from each other out to the level of the pulmonary bifurcation.

7.3.4 Trim the excess muscle on the right and left sides down to near the AV valves. All chordae are trimmed away, and a 2 mm edge of valve tissue along with the annulus is left intact. The atrial cuff generally extends 1 cm beyond the AV valves and consists of residual ventricular muscle and fat in the AV groove. The portion of the cuff in the left ventricular outflow tract consists of the residual anterior leaflet of the mitral valve and some aortic tissue. Most of the aortic tissue is trimmed away; however, some is left intact because it may present strong tissue for the sewing of the inflow connector. The great vessels are then separated from the remaining ventricular myocardium above the valvular level. The great vessels are separated from each other **(Figure 7-2)**.

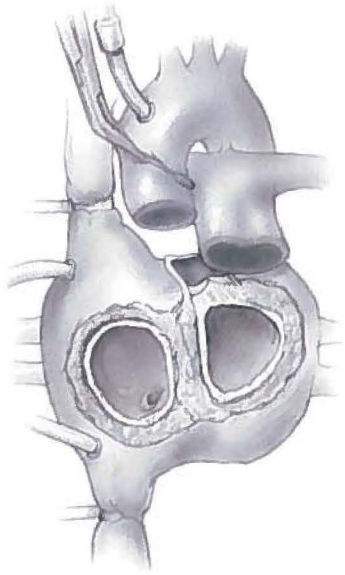


Figure 7-2 – Ventricles Removed

7.3.5 Over-sew the coronary sinus entrance into the right atrium **(Figure 7-3)**. This prevents backflow of blood through the coronary sinus and out to the cut vessels on the AV groove.

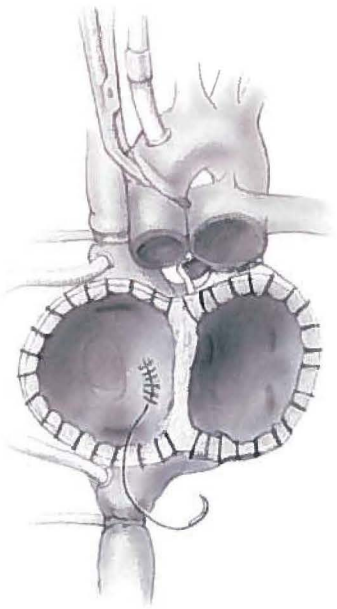


Figure 7-3 – Ligate Coronary Sinus

7.3.6 Three 15 by 20 cm sheets of membrane are used to create a neo-pericardium to prevent adhesions. On the right side, a sheet is anchored with non-absorbable suture to the pericardial reflection at the level of the superior vena cava, pulmonary veins and inferior vena cava. On the left side, a second sheet is sutured to the pericardial reflection just anterior to the left pulmonary veins. On the diaphragmatic side, a third sheet is sutured so as to cover the entire diaphragmatic pericardial surface. The three sheets are then folded upon themselves to keep them out of the operative field while the TAH-t is implanted.

7.4 Preparing the Atria

7.4.1 The outer walls of the entire right and left atrial cuff complex are encircled with Teflon felt buttresses. These are placed in such a way that they can be used for strengthening the anastomosis to the inflow connector and also to tamponade and control all possible bleeding from the AV groove portion of the connectors. These are cut to approximately 10-12 mm in width and are generally 10 cm in length. It most often takes at least two of these to extend around the entire atrial cuff. They are placed on the outer edge of the cuff and sewn in place with a running 3-0 polypropylene (**Figure 7-4**). A long needle (MH needle) is used to accomplish this and, after completing this, the left and right atrial cuffs are surrounded by Teflon felt buttresses.

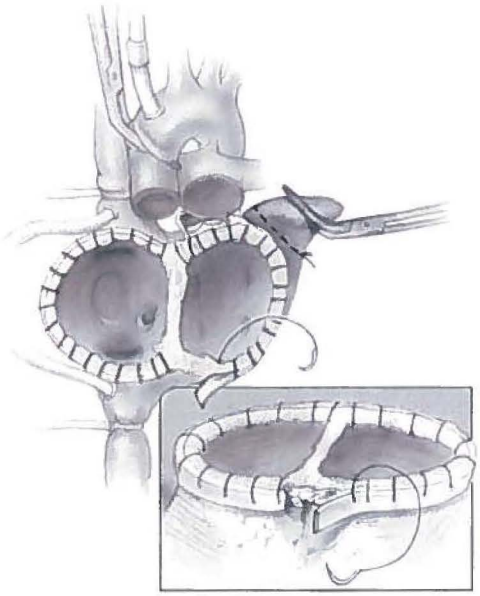


Figure 7-4 – Atrial Sutures

7.4.2 The atrial inflow connector is sewn first. It is inverted and placed inside the left atrial cuff on the lateral wall. 3-0 polypropylene is used with an MH needle with a running stitch, taking care to tailor the atrial cuff and the inflow connector into a single hemostatic suture line. The suture line includes both free walls of the atrium, buttressed with Teflon felt in the atrial septum, which has no buttressing material. A similar procedure is done with the right inflow connector. The connector is inverted and placed in the atrium, the suture line is run, and after completing both suture lines, the inflow connectors are returned to their normal positions (**Figure 7-5**).

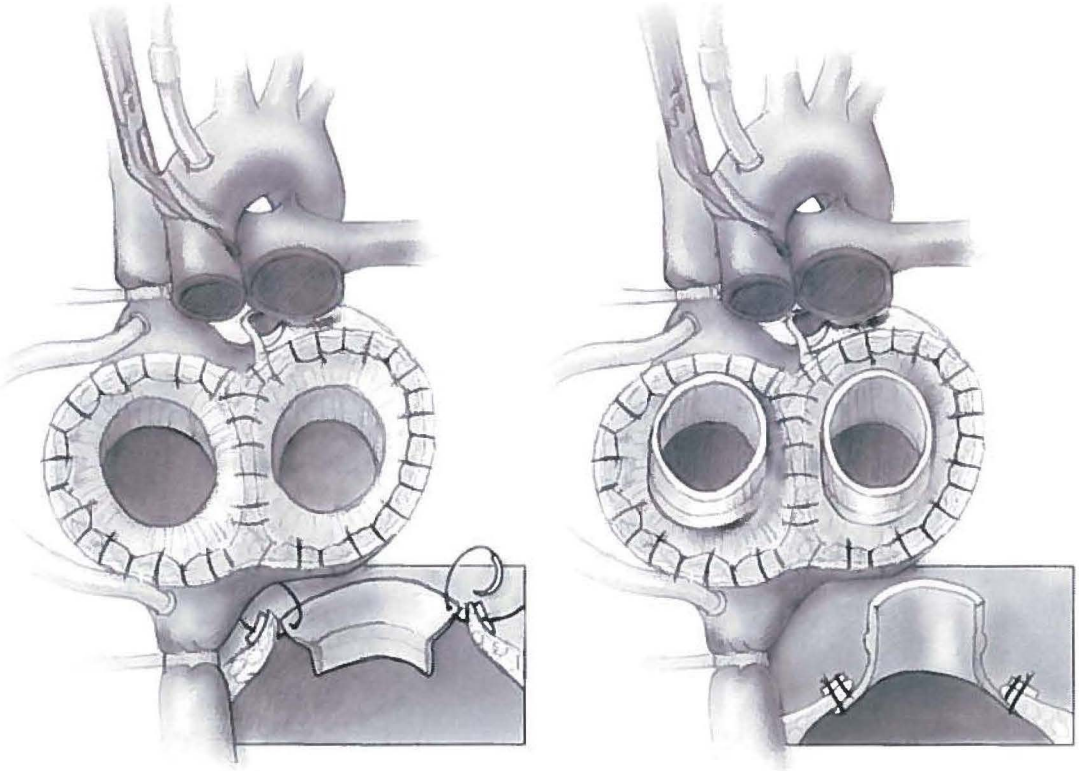


Figure 7-5 – Inflow Connector Inverted for Suturing (left), and Finished Normal Position (right)

7.4.3 Check for hemostasis with the plastic leak tester made to fit within the inflow connector **(Figure 7-6)**. A syringe (60-100 cc) is used to inject saline into a three-way stopcock connected with the tester to test the left atrial suture line. The surgeon places his hand posterior to the left atrium and compresses the right and left pulmonary veins, while the assistant injects saline mixed with a small amount of blood into the left atrium. An alternative test medium is methylene blue. Observe for leaks. A dental tool is used to break the seal between the tester and connector. If there are any leaks, sutures are placed at this time. On the right side, fluid is simply injected into the right atrium under pressure, since the inferior and superior venae cavae are already obstructed by the caval tapes. Again, closure of leaks with a 3-0 MH polypropylene suture is done at this time.

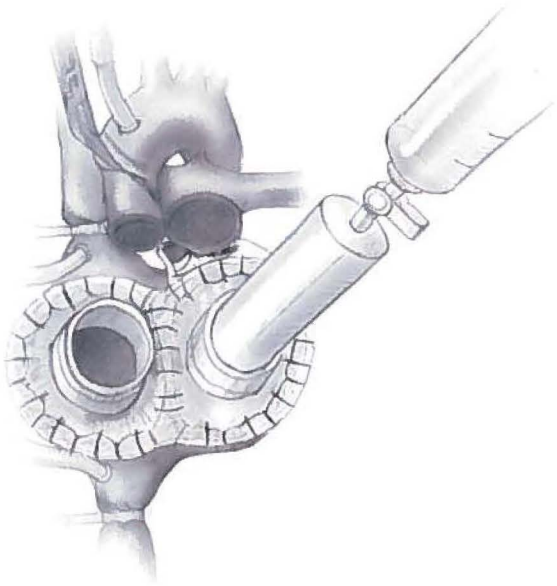


Figure 7-6 – Checking Inflow Connector for Hemostasis

7.5 Outflow Connectors

7.5.1 Great vessel connections are made. The pulmonary artery anastomosis is made first. The lengths of the outflow connectors are determined by placing the artificial ventricles in position within the pericardial cavity. Place the outflow connector between the aortic or pulmonic valve and its respective great vessel and measure the distance. Cut outflow connectors to the appropriate lengths, usually 3 to 5 cm.

7.5.2 The pulmonary artery anastomosis is made with a running 4-0 polypropylene suture in an end-to-end fashion, beginning with the lateral wall and running the back wall of the anastomosis from the inside (**Figure 7-7**).

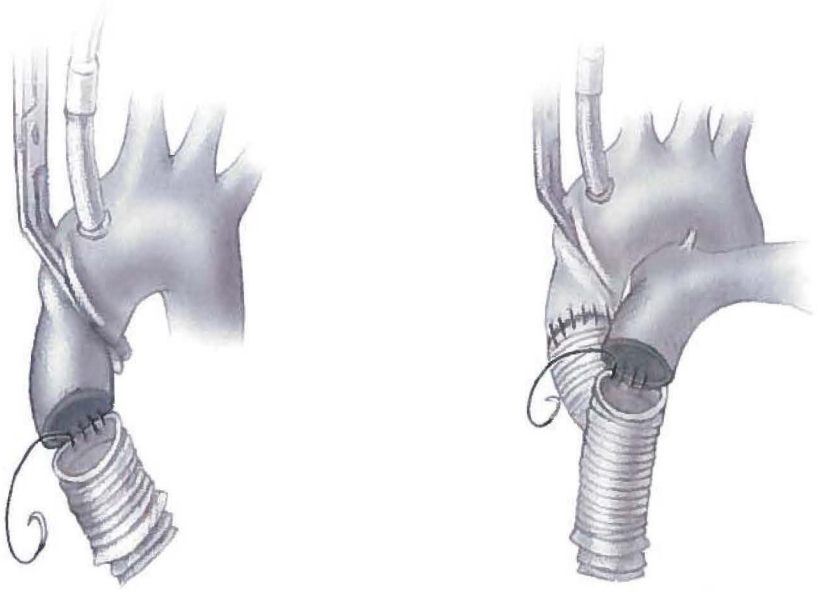


Figure 7-7 – Aorta (left) and Pulmonary Artery (right) Outflow Connector Suturing

7.5.3 A similar anastomosis is made with the aortic suture line **(Figure 7-7)**. Then, the outflow connector leak tester is inserted into the aortic outflow connector. Saline is injected under pressure, observed for leaks, and then any leaks are closed with a 4-0 polypropylene suture. The pulmonary artery needs to be cross-clamped in order to test the integrity of the pulmonary artery-to-connector anastomosis. The pulmonary artery/aortic tester is the same, but smaller, than the one utilized for the atrial inflow connector **(Figure 7-8)**.

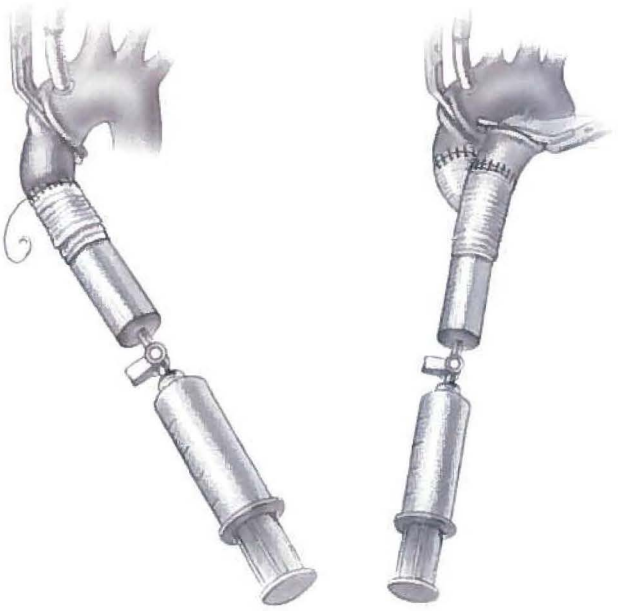


Figure 7-8 – Aorta (left) and Pulmonary Artery (right) Leak Testers

7.6 Connect Ventricles

7.6.1 Once adequate hemostasis of all suture lines is established, placement of the ventricles begins. First, the left ventricle is connected (**Figure 7-9**).

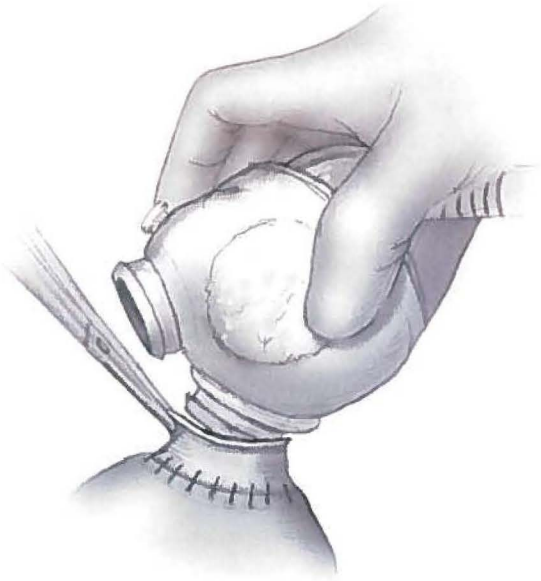


Figure 7-9 – Connect Ventricles

7.6.2 Grasp the left inflow connector with two large Mayo clamps placed side by side, with a good hold of the connector. The opposite side of the plastic fitting for the connector of the left ventricle is placed within the connector, and the operator pulls with the Mayo clamps and pushes the left ventricle into the inflow connector. The position in which the heart sits for the duration of the support of the patient is determined by the orientation of the left ventricle as it is placed into the left atrial inflow connector. Therefore, a careful assessment of exactly where the aortic outflow connector will connect to the left ventricle and the anticipated position of the left ventricle should be made before the connection of the atrial inflow connector is completed. Snap on the aortic outflow connector, taking care not to twist the connector or aorta. While this is being done, fill the left ventricle with saline through the aortic valve as well as the outflow connector. Once the connection is made, place the patient in a steep Trendelenburg position, and place large vent sites in the highest point of the aortic outflow connector and the aorta for removal of air.

7.6.3 Connect the right ventricle. Make the atrial connection first, again taking care with the orientation of the right ventricle, so that the direction of flow from the outlet valve is appropriate for the anatomy

of the patient. After the atrial connection is made, make the pulmonary outflow connection, again, taking care not to twist. Before connecting the pulmonary outflow connector graft, remove the chokers on the superior and inferior venae cavae. This allows a flow of blood into the right atrium and the right ventricle, and flushes air out as the connection to the pulmonary artery is made (**Figure 7-10**).

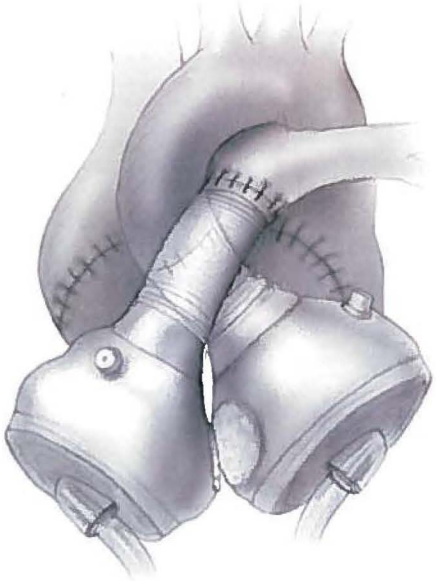


Figure 7-10 – TAH-t Final Position

7.6.4 Prepare the Driver prior to surgery as described in **Section 8.2, *Readying the Companion 2 Driver for Clinical Use***.

7.6.5 Perform Start Up of the Companion 2 Driver System as described in **Section 8.3, *TAH-t Startup Procedure***.

7.6.6 Attach the drivelines to the Driver.

7.6.7 Verify that the following parameters are programmed into the Driver:

- Rate: 1x
- % Systole: 50
- LDP: 180 mmHg
- RDP: 60 mmHg
- Right/Left Vacuum: 0 mmHg

7.6.8 Place the patient in a steep Trendelenburg position and slowly ventilate the lungs.

7.6.9 De-air both the left and right ventricles by delivering a single pulse from the Driver at the set pressure and vacuum. (Companion 2 operator presses the 1x button on the Driver for each pulse). Alternately, the rate can be set to a value desired by the surgeon to complete the de-airing process.

7.6.10 Agitate the ventricles, as well as the atria, to facilitate removal of air from the system. Use transesophageal echocardiography to help determine when the device has been completely de-aired.

7.6.11 As air is slowly removed from the TAH-t, and when directed by the surgeon, increase the pumping rate by pressing the rate "+" button to begin pumping at 40 bpm. Generally, this process takes about 10 minutes and should be done with patience and attention, to remove air from the artificial ventricles before the TAH-t takes over from the heart-lung machine. Decrease flow on the heart-lung machine temporarily to help move air through the lungs and into the TAH-t. Once satisfied that all the air is out of the TAH-t, close the vent sites, and begin full pumping at a rate of 120 bpm as the patient is weaned off the heart-lung machine.

7.6.12 The patient should be kept in steep Trendelenburg for an additional 15-20 minutes to ensure that any remaining air in the system does not cause neurologic complications. The stroke volumes will be low until the patient is completely weaned off cardiopulmonary bypass. As the perfusionist begins to slow venous return, TAH-t filling should increase.

7.6.13 As the table is flattened out, try to position the ventricles within the mediastinum. The pleura on both sides should not be opened and the pericardium should be left intact for closure.

7.6.14 In smaller patients, there may be a need to force the right ventricle under the left edge of the sternum. Care should be taken to examine the left pulmonary veins and the inferior vena cava for evidence of compression. This is facilitated with transesophageal echo.

7.6.15 Check for hemostasis. After protamine has been administered and hemostasis obtained, use towel clips to perform a trial closure of the sternum. If the fit of the device is judged to be adequate by hemodynamic stability and by transesophageal echo examination of the caval and pulmonary venous flows, reopen the chest and bring together the edges of the Gore-Tex sheets to form a tent or neo-pericardium. Take care to make a loose fit, without impinging upon the cavae and placing tension on the device. Prior to closure of the cephalic part of the neo-pericardium, pass a rectangular piece of Gore-Tex membrane around the proximal ascending aorta and anchor with non-absorbable suture. This provides a surgical plane at explant between the aorta and pulmonary artery to facilitate encircling and cross clamping the aorta.

7.6.16 Place one chest tube in the neo-pericardium and a second in the native pericardial space. Irrigate with antibiotic solution before closure. Close the sternum and remaining incision in a routine fashion. Check device output, central venous pressure, and device filling when the chest is closed, because chest closure may alter the anatomy, causing pressure on the left pulmonary veins, inferior vena cava, and occasionally the right pulmonary veins. If decreased flow is noted, reopen the chest and make changes in the position of the device. One possible change is to mobilize the diaphragmatic attachment of the pericardium, allowing the device to sit more leftward in the chest. This requires opening the left pleura, allowing the TAH-t to slightly migrate into the left pleural space. If decreased flow is still observed, the right ventricle may need to be anchored to a rib, using umbilical tape (**Figure 7-11**).

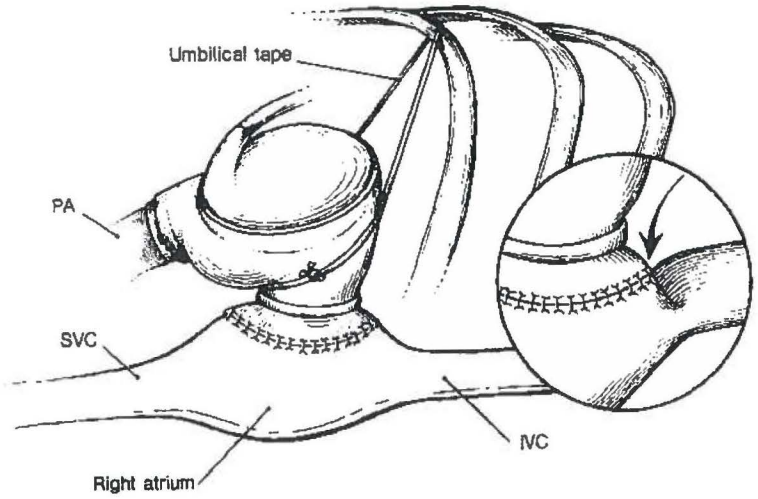


Figure 7-11 – Solution to a Fit Problem

Chapter 8. Companion 2 Driver System

The *SynCardia Companion 2 Driver System Operator Manual* contains detailed information on the setup and operation of the Companion 2 Driver System. It contains the following sections:

- Device Description
- Indications for Use
- Contraindications
- Warnings
- Precautions
- Companion 2 Driver
- Hospital Cart
- Driver Caddy
- Operating Modes – Surgical (O.R.) Environment
- Operating Modes – I.C.U. Environment
- Operating Modes – Ambulatory Mode
- List of Symbols
- Companion 2 Driver Operating Cautions
- Power Management
- Alarms and Notification
- Switching to Backup Companion 2 Driver
- Switching from the SynCardia CSS Console to the Companion 2 Driver System
- Switching from Companion 2 Driver System to the SynCardia CSS Console
- Switching from Companion 2 Driver System to the Freedom Driver System
- Equipment Maintenance and Care
- Unpacking and System Setup
- Companion 2 Driver System Specifications

8.1 Companion 2 Driver Operation Dos and Don'ts

- **Do** set backup Driver parameters to the same values as the primary Driver.
- **Do** keep wheel casters locked except for transport.
- **Do** connect the A/C power cord only to grounded mains outlets with ratings that match those given on the device identification label. Only connect the mains input of these components to suitable mains outlets complying with the electrical safety regulations of the respective country of use.
- **Do** protect all components from exposure to dampness and moisture. Do not store the Companion 2 Driver System in damp rooms.
- **Do** protect all components against temperatures lower than 10°C (50°F) and above 30°C (95°F), as well as against sudden temperature changes and overheating. Avoid exposing the components to direct heat radiation.
- **Do** protect all Companion 2 Driver System components against interference from strong electromagnetic fields (as generated by mobile/cell phones, magnetic resonance tomography equipment, etc.). This also applies to the Batteries not currently connected.
- **Do** ensure that the Companion 2 Driver System always receives an adequate amount of power. **Never disconnect both Batteries from the Driver at the same time.** Recharge depleted Batteries immediately.
- **Do** use only the power cords and Batteries supplied with the Companion 2 Driver System. Do not connect the Companion 2 Driver System to multiple-outlet adapters or mains extension cables.
- **Do** make sure that the Driver is not covered by textiles, clothing or similar items.
- **Do** protect all components against dirt and contamination (IP30 rating). Prevent foreign objects from falling or working their way into the connectors and ventilation slits.
- **Do** use only Batteries that you know are in full working order. Immediately replace Batteries that are not working correctly.
- **Do** protect the components against mechanical shocks, and ensure that they are not dropped.
- **Do** keep a backup Companion 2 Driver System ready for use and near the patient at all times.
- **Do not** operate or adjust the Companion 2 Driver System without proper training.
- **Do not** use a Driver outside of its planned maintenance cycle.

- **Do not** operate a Driver having only one functional compressor for any longer than is necessary to switch to a backup Driver.
- **Do not** leave the OR with the Driver set to O.R. Mode, because audible alarms are muted, and the system may be stopped by setting the rate to zero.
- **Do not** leave the key in the key switch while the Driver is operating. Remove the key once the Driver is turned on. Store in a location determined by the clinical staff.
- **Do not** use the Driver System in areas with explosive atmospheric conditions.
- **Do not** touch or manipulate the components with pointed or sharp-edged objects (surgical instruments, wire brushes etc.). Also be careful with clothing items, such as sharp-edged belt buckles.
- **Do not** let the Driver come into contact with any chemicals other than those permitted for disinfection.
- **Do not** place other objects on the Driver.

8.2 Readying the Companion 2 Driver for Clinical Use

8.2.1 Dock the Driver without External Batteries into the Hospital Cart. If necessary, this may be done with the help of another trained user.

8.2.2 Connect the Hospital Cart to a wall AC power source.

8.2.3 Insert two External Batteries into the Driver.

8.2.4 Connect the Driver to external air. If external air is not available, the Driver will operate with its internal compressors

8.2.5 Turn the Driver to the ON position using the key, and then remove the key and store in a location determined by the clinical staff.

8.2.6 Immediately upon start-up, the Driver will perform several self-checks to verify that all the internal electronics are functioning properly. The Driver will operate at the default parameters until the software is fully loaded. It will then operate at the previously settings in Ambulatory Mode.

8.2.7 Change from Ambulatory Mode to O.R. Mode using the password.

8.2.8 Perform System Check – Select MENU, SYSTEM, and SYSTEM CHECK, then follow the onscreen prompts.

8.2.9 Enter data for the new patient's profile.

8.2.10 Set the startup parameters in O.R. Mode to the following values:

- Rate: "--" indicates single pulse mode
- % Systole: 50
- LDP: 180 mmHg

- RDP: 60 mmHg
- Right/Left Vacuum: 0 mmHg
- **NOTE**: When in O.R. Mode, audible alarms are always muted.

8.2.11 Before moving the Driver (and Hospital Cart) to the Operating Room, moisten a clean cloth with an antibacterial agent and wipe down all exterior surfaces of the Hospital Cart.

8.2.12 Do not spray any cleaning agent directly on the Driver or Hospital Cart.

8.2.13 Move the Driver (and Hospital Cart) into the O.R. and plug the Hospital Cart into a wall outlet.

8.3 TAH-t Startup Procedures

8.3.1 Position the rear side of the Hospital Cart within driveline length of the patient's chest.

8.3.2 Lock the casters (wheels).

8.3.3 Verify that the Driver is in O.R. mode with the following values:

- Rate: "--" indicates single pulse mode
- % Systole: 50
- LDP: 180 mmHg
- RDP: 60 mmHg
- Right/Left Vacuum: 0 mmHg
- **NOTE**: When in O.R. Mode, audible alarms are always muted.

8.3.4 Attach drivelines to Driver.

8.3.5 When instructed by the surgeon, deliver a single pulse at the set pressure and vacuum by pressing the 1x button to de-air both the left and right ventricles. Continue to deliver single pulses by pressing the 1x button as directed by the surgeon until all air is out of the system. Alternately, the rate can be set to a value desired by the surgeon to complete the de-airing process. After ventricles are de-aired and verified by transesophageal echo, await instructions from the surgeon to continue.

8.3.6 Following de-airing and when directed by the surgeon, press the rate "+" button to begin pumping at 40 bpm.

8.3.7 If there is a need to stop the Driver, the drivelines can be disconnected from the Driver using the single connector to immediately cease TAH-t pneumatic support. Alternately, the Driver may be switched to the OFF position, but the System must complete the boot process before settings can be adjusted.

8.3.8 When the surgeon is ready to wean the patient from cardiopulmonary bypass, increase the rate to 120 bpm. Pressing

the "+" button will increase rate by 1 BPM. Press and hold the "+" button to increase rate in 10 BPM increments.

8.3.9 Stroke volumes will be low until the patient is completely weaned from cardiopulmonary bypass. As the perfusionist begins to slow venous return, TAH-t filling should increase.

8.3.10 Pneumatic drive ejection pressures should be set to achieve full ejection. Monitor the pressure tracings displayed on the Hospital Cart Display to assure the right drive pressure is set to overcome the pulmonary systolic pressure, and the left drive pressure is set to overcome the aortic systolic pressure.

8.3.11 The fill volumes will be approximately 45 ± 5 milliliters until volume is added and vacuum is applied.

8.3.12 Do not apply vacuum until after chest is completely closed.

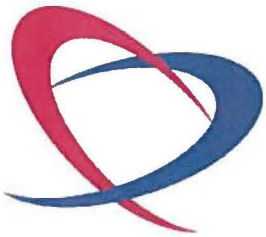
8.3.13 The TAH-t Rate should be set on the Hospital Cart Display to achieve a stroke volume between 50 and 60 milliliters. TAH-t Rate is typically between 110 - 130 bpm.

8.3.14 Prior to moving to ICU, press MENU on the Driver, then MODE and enter ICU Mode to enable audible alarm functions of the Driver, to add additional security for changing operating parameters, and to prevent changes of rate to a single pulse mode or other non-therapeutic settings (e.g., 40 bpm).

8.3.15 When moving patient to ICU from the OR, the Hospital Cart with the docked Driver can be placed at the foot of the bed, or the Driver can be docked into a Driver Caddy, or can be placed on the patient's bed.

8.3.16 In ICU, continue to monitor Driver settings to ensure partial fill volumes and full eject and adjust as necessary.

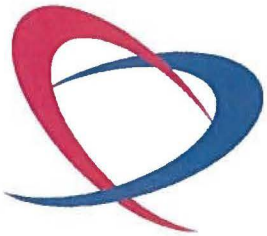
8.3.17 When the patient is ready to be moved from ICU to the Step Down Unit, change user mode to Ambulatory Mode to prevent unauthorized changes to device settings.



Chapter 9. Explantation Procedures

Explantation of the TAH-t should be handled like any other redo cardiac procedure. Great care should be taken in the separation of the sternum from the TAH-t, the great vessel connector, and the drivelines. Explantation may be easier if the TAH-t is covered with a Gore-Tex membrane.

Initiate cardiopulmonary bypass with dual caval cannulation with tourniquets. Cross-clamp the aorta, and turn off the TAH-t System. Separate the artificial ventricles from the atrial inflow cannula. Amputate the great vessels outflow connectors at the level of the connector/great vessel anastomosis. Transect the artificial ventricles at the base to the cannula connection, and remove the TAH-t from the operating field. Pull the cannulae through the skin. The remaining atria inflow connectors are still in the remaining portion of ventricular muscle where they were initially sutured. Remove them by transecting the AV groove throughout. Trim the remaining atria and great vessels to accept the donor heart.



Chapter 10. System Components

10.1 SynCardia TAH-t System

The 70cc TAH-t System is comprised of the following:

- Implant Kit - Part # 500101 (Sterile)

  Contains left artificial ventricle, right artificial ventricle, two inflow connectors, two outflow connectors, and an ancillary pack with inflow pressure test plug, outflow pressure test plug, and locking ties (all sterile). Companion 2 Drivelines are not included in the 70cc Implant Kit. All sterile components are packaged in double aseptic transfer packages.

- Surgical Spares Kit - Part # 500177 (Sterile)

  Contains inflow connector, outflow connector, inflow pressure test plug, outflow pressure test plug, and locking ties.

- External Pneumatic Driver:

  Companion 2 Driver System – Part # 397002-001 (non-sterile).

10.2 Companion 2 Driver System

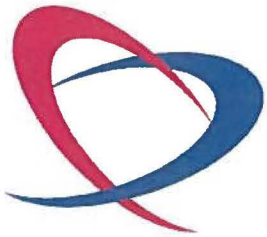
The Companion 2 Driver System is comprised of the following components:

- Driver (plus one additional backup Driver) – Part # 397002-001
- 2 Batteries (plus two additional Batteries for backup Driver) - Part # 293001-001
- Hospital Cart - Part # C-400002 / Part # 397003-001
- Caddy - Part # C-400003 / Part # 397001-001
- AC Power Cord - Part # 197053
- Drivelines - Part # C-400008 / Part # 193002-001
- Optional Hand Pump – Part # 397004

Chapter 11. List of Symbols

Table 11-1 – Symbols Used in TAH-t Labeling

Symbol	Description
	Do not use if package is damaged



Appendix A – Patient Selection and Management

Management and coordination of successful TAH-t support requires a multidisciplinary team that has experience with circulatory support systems. Teams can include surgeons, cardiologists, heart transplant coordinators, perfusionists, engineers, nurses, cardiac rehabilitation therapists and coagulation specialists.

The following is a report of the experience of one of the largest clinical site users, University Medical Center, Tucson, Arizona.

Patient Selection

Successful bridge to transplant with the TAH-t involves selecting patients who are transplant eligible and who additionally are assessed in two main areas: 1) evaluation of fit of the TAH-t in the patient's chest, and 2) evaluation of the potential for reversal of any end organ dysfunction.

Once the TAH-t is implanted, and there are no fit issues, flow is maximized through the TAH-t.

The TAH-t is generally specified for patients with body surface areas of 1.7 m^2. At a cardiac index of 2.5 $l/min/m^2$, the calculated flow would be 4.25 liters/min. This is the flow used to simulate hypotensive conditions tested during product reliability testing.

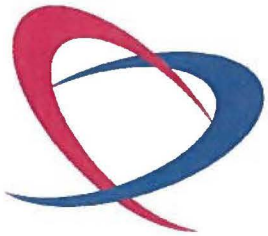
With normalized hemodynamics, device outputs remain relatively constant, changing as the CVP fluctuates. This "Starling-like response" (where an increase in CVP fills the TAH-t with more volume, which is ejected on the next beat, increasing device output), requires no controller adjustments. Constant device output and high flow under normal CVP provides washing of the artificial ventricles.

Antithrombotic Therapy

The level of anticoagulation will vary depending on the patient's coagulation status. Typically, patients supported with the TAH-t require systemic antithrombotics similar to that used for patients with mechanical valves.

Driveline Exit Site Management

Take care to keep driveline exit sites clean and dry. Infections should be treated according to hospital protocol.



Appendix B – Outline of Training Program

Operation of the TAH-t System should only be undertaken by personnel trained in accordance with the SynCardia Certification Program. The program will include the following topics:

(1) Indications and Contraindications

(2) System Overview

(3) Implant Procedures

(4) Operation of the Drive Systems

(5) Explant Procedures

(6) Patient Management

(7) Summary of Clinical Studies

(8) Animal Procedure – a minimum of one implant needs to be performed.

(9) Practical Experience - Physicians will be required to minimally view one live implant procedure or have their first procedure proctored. SynCardia will maintain centers of excellence where surgeons may view implantations. Proctors will be made available by SynCardia for surgical teams during their first case.

(10) Patient Management for Discharge

Appendix C – Materials Matrix

The TAH-t ventricle components are manufactured from the raw materials as defined in **Table C-1**. The artificial ventricles and drivelines have met the test requirements of ISO 10993, *Biological Evaluation of Medical Devices.*

Table C-1 - TAH-t Patient Contacting Materials Matrix

Component	Material
Ventricle and diaphragm	Segmented polyurethane
	Nylon
Inflow connector	Segmented polyurethane
	Polyester fabric
Outflow connector	Segmented polyurethane
	Polyester material
Valves	Titanium and pyrolytic carbon
Cannulae	Polyvinyl chloride tubing

TAB 4

21 CFR §814.20(b)(3)
SUMMARY OF SAFETY AND EFFECTIVENESS

SynCardia Systems, Inc.
CardioWest temporary Total Artificial Heart (TAH-t)

Premarket Approval (PMA) Application P030011

SynCardia Systems, Inc.
1992 E. Silverlake Road
Tucson, Arizona 85713

I. GENERAL INFORMATION

Device Generic Name:	Total Artificial Heart
Device Trade Name:	CardioWest temporary Total Artificial Heart (TAH-t)
Applicant's Name and Address:	SynCardia Systems, Inc. 1992 East Silverlake Road Tucson, Arizona 85713
PMA Application Number:	P030011
Date of Panel Recommendation:	3-17-04
Date of Notice of Approval to the Applicant:	10-15-04

II. INDICATIONS FOR USE

The SynCardia Systems, Inc., CardioWest temporary Total Artificial Heart (hereinafter called the TAH-t) is indicated for use as a bridge to transplantation in cardiac transplant-eligible candidates at risk of imminent death from biventricular failure. The CardioWest TAH-t System is intended for use inside the hospital.

III. CONTRAINDICATIONS

Patients who are not cardiac transplant eligible.

Patients who do not have sufficient space in the chest area vacated by the natural ventricles. Generally this includes patients who have body surface areas $<1.7m^2$, or who have a distance between the sternum and the 10^{th} anterior vertebral body measured by computed tomography imaging (CT scan) $\leq$ 10 cm.

Patients who cannot be adequately anticoagulated on the TAH-t.

IV. WARNINGS AND PRECAUTIONS

All Warnings and Precautions can be found in the attached labeling.

V. DEVICE DESCRIPTION

The SynCardia CardioWest TAH-t system is a pulsatile biventricular device that is placed after the native ventricles are excised. The implantable device consists of two artificial ventricles, each made of a semi-rigid polyurethane housing with four flexible polyurethane diaphragms separating the blood chamber from the air chamber. These diaphragms allow the ventricles to fill and then eject blood when compressed by air from the external drive console. Mechanical valves mounted in the inflow (27 mm) and outflow (25 mm) ports of each artificial ventricle control the direction of blood flow. The maximum dynamic stroke

volume of each artificial ventricle is 70 ml, which allows for generating a flow rate up to 9.5 l/min. The right artificial ventricle is connected via the right atrial inflow connector to the right atrium and via the pulmonary artery outflow cannulae to the pulmonary artery. The left artificial ventricle is connected via the left atrial inflow connector to the left atrium, and via the aortic outflow cannulae to the aorta. Each artificial ventricle's driveline conduit is tunneled through the chest. The driveline conduit is covered with velour fabric on its external surface to promote tissue growth. The right and left driveline conduits are attached to seven-foot drivelines that connect to the back of the external drive console.

The console includes a monitoring computer that provides noninvasive diagnostic and monitoring information to the user. Device pumping rate, noninvasive dynamic stroke volumes, and calculated cardiac outputs are displayed on a beat-to-beat basis. Drive pressure and flow waveforms, along with cardiac output trends are provided. Patient related alarms (e.g., low cardiac output) are also displayed on the computer screen. A separate alarm panel on the console provides information on critical drive pressure and backup systems. All alarms generate audio and visual feedback to the user.

A backup air supply (two air tanks) and electrical power (backup power supply and console battery) are automatically activated if the external compressed air and /or AC power are interrupted. This can occur during patient transport or in the event of a failure in the hospital's air or electrical supply.

The controller is the major component of the external console, and supplies pulses of pneumatic pressure to the right and left drivelines, which connect into the air chambers of the respective implanted artificial ventricles. These pulses cause the diaphragms to distend and thereby eject blood from the right artificial ventricle into the pulmonary circulation and from the left artificial ventricle into the systemic circulation.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

One device, the Thoratec Ventricular Assist Device System, is approved for use as a bi-VAD device. The TAH-t is the only device tested that replaces a patient's native ventricles and valves so as to completely take over pumping of blood to both the pulmonary and systemic circulation, and bridge the patient to transplant.

VII. MARKETING HISTORY

Under the authority of 21 CFR §801(e), SynCardia has permission to export, and has distributed the CardioWest Total Artificial Heart to Canada, France, and Germany. The SynCardia CardioWest TAH-t has not been withdrawn from marketing for any reason related to safety and effectiveness of the device.

VIII. ADVERSE EFFECTS

Adverse events collected for all implant patients while on the TAH-t are presented in descending order below. The adverse events represent 19.7 device years of experience while on the device awaiting transplant, and 25.0 man years from date of implant through 30 days post transplant.

Table 1
Incidence of Adverse Events by Decreasing Frequency

	All Patients During Implant Period		All Patients from Implant to 30-days Post Transplant	
Adverse Event	**Number of Events**	**Number (%) of Patients n=95**	**Number of Events**	**Number (%) of Patients n=95**
Any Adverse Event	478	88 (92.6%)	589	93 (97.9%)
Infection	142	66 (69.5%)	172	73 (76.8%)
a. respiratory	58	44 (46.3%)	70	51 (53.7%)
b. urinary tract	32	25 (26.3%)	37	27 (28.4%)
c. device/driveline	18	16 (16.8%)	18	16 (16.8%)
Bleeding	71	42 (44.2%)	102	59 (62.1%)
Respiratory Dysfunction	53	29 (30.5%)	61	34 (35.8%)
Hepatic Dysfunction	34	33 (34.7%)	37	35 (36.8%)
Neurological Event	27	21 (22.1%)	35	26 (27.4%)
a. strokes	11	10 (10.5%)	14	13 (13.7%)
b. TIA	4	3 (3.2%)	4	3 (3.2%)
Renal Dysfunction	28	26 (27.4%)	34	29 (30.5%)
a. elevated creatinine	3	3 (3.2%)	3	3 (3.2%)
b. dialysis	25	24 (25.3%)	31	27 (28.4%)
Reoperation	21	19 (20.0%)	31	23 (24.2%)
Device Malfunction	19	16 (16.8%)	19	16 (16.8%)
a. Driveline kink/leaks	16	14 (14.7%)	16	14 (14.7%)
b. Controller	1	1 (1.1%)	1	1 (1.1%)
c. Air tank	1	1 (1.1%)	1	1 (1.1%)
d. Diaphragm	1	1 (1.1%)	1	1 (1.1%)
Reduced Blood Pressure	30	18 (18.9%)	33	22 (23.2%)
Peripheral Thromboembolism	14	9 (9.5%)	18	13 (13.7%)
a. visual	6	5 (5.3%)	6	5 (5.3%)
b. extremities	5	4 (4.2%)	8	7 (7.4%)
c. abdominal	3	2 (2.1%)	4	3 (3.2%)

	All Patients During Implant Period		All Patients from Implant to 30-days Post Transplant	
Adverse Event	**Number of Events**	**Number (%) of Patients n=95**	**Number of Events**	**Number (%) of Patients n=95**
Reduced Cardiac Index	13	9 (9.5%)	16	12 (12.6%)
Technical/Procedural	11	3 (3.2%)	11	3 (3.2%)
Miscellaneous	5	5 (5.3%)	10	9 (9.5%)
Fit Complication	5	5 (5.3%)	5	5 (5.3%)
Hemolysis	5	4 (4.2%)	5	4 (4.2%)

The adverse events for all patients while on the total artificial heart represented 7079 days on the device. This equates to an adverse event rate on the device of 0.067 events per day while on the device.

The adverse events for all patients from the time of total artificial heart implant to 30 days post transplant (30 days after the implanted TAH-t has been removed) represents an additional 1931 days, for a total time to collect adverse events of 9010 days. The event rate for all implanted patients out to 30 days post transplant is comparable, at 0.065 events per day.

Infections were the largest contributing category to overall adverse events. The majority of infections (150/172 [87.2%]) did not affect patient outcome. Most were respiratory infections followed by genitourinary infections which occurred the first few weeks following implant. Driveline infections were predominantly superficial skin infections treated with routine dressing changes.

Bleeding was related to the surgical implant and transplant procedures. In some cases, reoperations for bleeding (30/102 [29.4%]) were also required for excessive bleeding around the heart or lungs. Fifty-nine [57.8%] of the 102 bleeding events occurred during the first 3 weeks after implant with another 30 events (29.4%) occurring within 2 days after transplant.

Respiratory dysfunction was also surgically related with most events (40/61 [65.6%]) occurring during the first 3 weeks following the implant surgery and 8/61 (13.1%) occurring after the transplant surgery. Hepatic and renal dysfunction occurred in the first 3 weeks following the implant. By 4 weeks, hepatic and renal markers were at normal levels.

Thirty-five neurologic events occurred in 26 implant patients during the implant and 30-days post transplant periods. Fourteen strokes occurred in 13 patients during the implant to

30-days post transplant period. One stroke temporarily affected patient outcome, and that patient was successfully transplanted after 332 days on the device. Other neurologic events were encephalopathy (6/35 [17.1%]), seizures (7/35 [20.0%]), transient ischemic attacks (4/35 [11.4%]), loss of consciousness (2/35 [5.7%]) and related to metabolic imbalances (2/35 [5.7%]).

There were 11 driveline kinks that occurred when patients rolled over or sat on their drivelines, and 5 driveline leaks. A design change was implemented to relocate the wire reinforcement within the driveline. There have been no reports of driveline leaks since the change was implemented. One malfunction, a diaphragm tear, was a primary cause of death. .The patient had hemodynamic insufficiency, was carefully monitored, and on post-operative day 115, a clot caused cardiac output to decrease, requiring removal of a large hemo-pneumothorax. The family refused another implant and the patient developed multi-organ failure and died on day 124. Although extensively investigated, the cause of the failure was never determined and could never be duplicated. There have been no additional instances of diaphragm tears found during production or experienced clinically, since the incident.

Reduced blood pressure was secondary to sepsis (12/33 [36.4 %]), volume depletion 11/33 [33.3%]), medication (1/33 [3.0%]) and hematuria (1/33 [3.0%]).

All technical/procedural events (11/11 [100%]) were related to a central catheter obstruction of the artificial valve within the TAH-t. Labeling has been modified to include a warning based on these clinical events. The warning advises physicians to not allow any catheter near the left or right inflow valves.

IX. SUMMARY OF NON-CLINICAL LABORATORY TESTS

A. Biocompatibility/Sterilization

The implantable hearts were sterilized by the validated EtO sterilization cycle, extracted and tested in accordance with ISO 10993, *Biological Evaluation of Medical Devices*, test methods, and in accordance with Good Laboratory Practices. Results of the testing are summarized below.

Table 2
Biocompatibility Testing

Test Performed	Result
Cytotoxicity	Non-cytotoxic
Acute Systemic Toxicity	No systemic toxicity
Subchronic Toxicity	No histological evidence of subchronic toxicity
Ames Mutagenicity	Non-mutagenic
Chromosomal Aberration Assay	No induced chromosomal aberrations
Mouse Micronucleus Mutagenicity	Non-mutagenic
Pyrogen	Nonpyrogenic
Sensitization	Non-sensitizing
Hemocompatibility	Hemocompatible

B. In-vitro Studies

1. *In-vitro* Characterization

In-vitro characterization of the TAH-t on a mock circulatory loop demonstrated the performance of TAH-t under normal, hypotensive and hypertensive simulated operating conditions as indicated below.

Table 3
Conditions for Mock Circulation Testing

Setting/Parameter	Hypotensive	Normal	Hypertensive
BPM ± 5	80	120	140
% systole ± 5	55	50	60
LDP ± 15 mmHg	150	200	280
RDP ± 15 mmHg	40	75	135
Vacuum ± 5 mm Hg	none	10	15

The TAH-t provided a range from 2.6-9.5 l/min flow, which is sufficient to support total circulation under the expected clinical conditions.

2. *In-vitro* System Testing

Laboratory testing was performed to demonstrate that the TAH-t system met its intended functional specifications. Testing included pull tests and torque tests on the ventricle-to-connector joints and drivelines, and sterility and packaging testing on the implantable components of the system. Console testing included controller performance of alarms, system connections, battery longevity, electrical safety and electro-magnetic compatibility. Software verification and validation was performed and back-up air and power performance were verified under simulated use conditions.

C. Reliability

The purpose of reliability testing is to determine with reasonable assurance, how long a given device will perform as intended, without failure.

Three separate sets of *in vitro* reliability testing were conducted. In one test, four TAH-t units were run for a period of 180 days. During this time there were no failures or abnormalities observed.

In a second *in vitro* reliability trial initiated in December 1998, four TAH-t units were tested in a "run to failure" study design and are ongoing. To date, there have been no failures or abnormalities observed.

A third test was initiated using three TAH-t units which had expired their 3 year sterilization expiration date. This provided information about the effects of long-term storage on the fatigue resistance properties of the TAH-t. To date, there have been no failures or abnormalities observed.

In conclusion, a total of eleven units have been run for various lengths of time over the last six years with no device-related failures. The cumulative number of days used for calculation was 6715 and there have been no failures or signs of appreciable wear observed. When the 11 units are used to calculate reliability with a 90% confidence, the reliability at 30, 60 and 365 days is as reported in the table below.

Table 4
Reliability Test Results with 90% Confidence

# days run	MTBF*	Reliability in number of days run		
		30	60	365
6715	2916	0.99	0.98	0.88

X. SUMMARY OF CLINICAL STUDIES

A. Study Objective

The purpose of this study was to demonstrate that the CardioWest Total Artificial Heart is safe and effective in providing circulatory support as a bridge to cardiac transplantation in patients with biventricular failure. Bridge to transplant is defined as the use of a circulatory support device to maintain viability for transplantation until a donor organ is procured.

B. Study Design

The study was approved under IDE G920101 as a non-randomized, multi-centered trial with both historical and concurrent controls. Patients were transplant candidates who were at risk of imminent death from biventricular heart failure. The overall objective of this study was to determine if the TAH-t was safe and effective for bridging patients to cardiac transplantation. A total of 95 patients were enrolled. Of these, 81 formed the core implant group and an additional 14 patients did not meet study entrance criteria and were considered an out-of-protocol cohort, treated under compassionate use. IRB acknowledgments were obtained for each patient. The data used to demonstrate safety and effectiveness were collected from patients enrolled at five U.S. investigational sites.

1. Effectiveness Parameters

Treatment success was defined as patients who, at 30 days post transplant, were 1) alive; 2) New York Heart Association Class I or II; 3) not bedridden; 4) not ventilator dependent; and 5) not requiring dialysis. Overall survival, hemodynamics and kidney and liver end organ function were secondary effectiveness endpoints.

2. Safety Parameters

Patients were clinically assessed and adverse events were evaluated for safety.

C. Study Protocol

1. Inclusion Criteria

Patients who met all of the following inclusion criteria were eligible for the study:

- Signed informed consent
- Eligible for Transplant
- New York Heart Association Functional IV

- Body surface area 1.7-2.5 m^2, or have a distance between the sternum and the 10^{th} anterior vertebral body measured by computed tomography imaging (CT scan) ≥ 10 cm.
- Hemodynamic insufficiency demonstrated by A or B below:

  A: Cardiac index ≤2.0 l/min/M^2 and one of the following:
  Systolic arterial pressure ≤90 mm Hg
  Central venous pressure ≥18 mm Hg

  B: Two of the following:
  Dopamine ≥ 10 μg/kg/min
  Dobutamine ≥ 10 μg /kg/min
  Epinephrine ≥ 2 μg /kg/min
  Isoproterinol ≥2 μg /kg/min
  Amrinone ≥ 10 μg /kg/min
  Other drugs at maximum levels
  Intra-aortic balloon pump (IAPB)
  Cardiopulmonary bypass (CPB)

2. *Exclusion Criteria*

   Patients with any of the following conditions were excluded from the study:

   - Use of any ventricular assist device
   - Pulmonary Vascular Resistance ≥ 8 Wood (640 Dynes-sec/cm5).
   - Dialysis in previous 7 days
   - Serum Creatinine ≥ 5 mg/dl
   - Cirrhosis with Bilirubin ≥ 5 mg/dl
   - Cytotoxic antibody ≥ 10%

3. *Treatment Procedures*

   All patients were screened for study eligibility. The treatment group met eligibility criteria within 48 hours of the implant procedure, signed an informed consent and received a TAH-t implant.

4. *Term of Study*

   Patients were followed through the primary endpoint of 30 days post transplant, and then monitored for survival annually.

D. Comparison Population

A comparison group was initially identified by retrospective review during a time period when the TAH-t was not available to the participating centers. Analysis of the baseline data from this group of patients revealed they were not comparable to

the treatment group. An imbalance in the year of implant and in multiple baseline covariates made statistical comparisons inappropriate. Therefore, a survival to transplant performance goal (65%) that had been developed for bridge to transplant in univentricular devices (LVADs) was used as a guideline. It should be noted that the adverse events were not compared to a performance goal due to different definitions. The LVAD performance goal was established from a literature search of articles published in 1997 or after for the bridge to transplant indication. The criteria for inclusion were: at least 20 adult patients, original data, wide geographic distribution, and enough detailed data to determine the results in LVAD adult patients. The criteria for exclusion were: duplicate papers reporting the same population, registries, meta-analyses, RV support at initial implant, and cardiogenic shock patients.

E. Description of Study Population

There were 81 patients entered into the core treatment group. The patients were predominantly male (86%) with average age of 51 (range 16-67), and average body weights and surface areas of 85.3 kg and 2.0 m^2. All patients were NYHA functional Class IV at the time of enrollment. The etiology of the heart disease was ischemic (53%) or idiopathic (47%).

Patients enrolled in the clinical trial had irreversible biventricular failure and were not candidates for VAD devices as evidenced by the presence of at least one of the following:

Patients with Irreversible Biventricular Failure and Contraindications to VAD Use	n
Refractory Arrhythmias/Unresuscitatable cardiac arrest	25
Hypokinetic right/left/global ventricle	23
Aortic regurgitation, stenosis, prosthesis	13
Massive myocardial infarction or direct myocardial injury that affects technical insertion of a VAD through the ventricle.	10
Failure to wean from cardiopulmonary bypass with biventricular injury	4
Left Ventricular/Right Ventricular/Mural Thrombus	3
Ventricular Septal Defect	3

Analysis of baseline covariates at the completion of the study indicated that the control and core implant patients were not statistically comparable. No valid statistical comparisons could be made between the two groups. Therefore, the results for the control group are not included in this summary.

The study was designed as a multi-institutional study. The following distribution of implants occurred for the core patients.

Table 5 Enrollment by Center

Center Code	Center	Number (%) Core Patients
UMC	University Medical Center, Tucson, AZ	58 (72%)
LOY	Loyola University Medical Center, Chicago, IL	13 (16%)
LDS	LDS Hospital Salt Lake City, UT	8 (10%)
STL	St. Luke's Medical Center Milwaukee, WI	1 (1%)
UPM	Univ. of Pittsburgh Medical Center Pittsburgh, PA	1 (1%)
	Total	***81***

No gender requirements were identified for inclusion into the trial. The United Network for Organ Sharing (UNOS) August 1, 2001 database of all patients receiving heart transplants, heart-lung transplants or multiple organ transplants, divides gender into 73.3% males and 26.7% females for cardiac transplants.. For the 64 patients who received a heart transplant in this trial, 86.4% were males vs. 13.6% females, indicating similar characteristics as the UNOS data.

The inclusion criteria were broad and it is recognized that the diagnosis of RV failure is difficult. The following are the inclusion criteria for the study and the prevalence of patients meeting each part of the inclusion criteria:

- Hemodynamic insufficiency demonstrated by A or B below:

  A: Cardiac index ≤ 2.0 l/min/M^2 and one of the following:
  Systolic arterial pressure ≤ 90 mm Hg
  Central venous pressure ≥ 18 mm Hg

  B: Two of the following:
  Dopamine ≥ 10 μg/kg/min
  Dobutamine ≥ 10 μg /kg/min
  Epinephrine ≥ 2 μg /kg/min
  Isoproterinol ≥ 2 μg /kg/min
  Amrinone ≥ 10 μg /kg/min
  Other drugs at maximum levels
  Intra-aortic balloon pump (IAPB)
  Cardiopulmonary bypass (CPB)

Table 6
Inclusion Criteria of Core Implant Patients

Inclusion Criteria Met	Number of Patients (%) n=81
Only A (SAP <90 or CVP >18)	25 (30.9%)
Only B (drugs, IABP, CPB)	30 (37.0%)
Both A and B	26 (32.1%)

Baseline characteristics for the core patients are provided in the table below.

Table 7
Baseline Demographics, Risk Factors and Clinical Characteristics for Core Implant Patients

Characteristic	n=81
Age (years) Mean ± SD	51.1 (10.3)
Male	70 (86.4%)
Height (mean in cm) ± SD	176.2 (11.1)
Weight (mean in kg) ± SD	85.3 (13.2)
BSA (mean as m^2) ± SD	2.0 (0.18)
NYHA Class IV	81 (100.0%)
Cardiac index L/min/m^2 ± SD	1.9 (0.5)
Etiology – Ischemic	43 (53.1%)
Etiology -Non-ischemic (idiopathic)	38 (46.9%)
History of smoking	44 (54.3%)
History of excessive alcohol use	37 (45.7%)
Hypertensive	26 (32.1%)
Prior cardiac arrest	30 (37.0%)
Anticoagulated on entry	38 (46.9%)
Insulin-dependent Diabetes Mellitus	5 (6.2%)
Non- insulin-dependent Diabetes Mellitus	15 (18.5%)
Entry on Cardiopulmonary bypass	15 (18.5%)
Entry on intra-aortic balloon pump	29 (35.8%)
Entry with ventilator	34 (42.0%)
Entry obtunded/drowsy	28 (34.6%)

Characteristic	n=81
Prior mediastinal surgery	31 (38.3%)
Prior percutaneous angioplasty	12 (14.8%)
Pacemaker	10 (12.3%)
Automatic implantable cardioverter defibrillator	24 (29.6%)

Baseline hemodynamics, hematology and blood chemistry for the core implant group is presented below. At entry, 15 patients were supported by cardiopulmonary bypass and 29 patients were supported on intra-aortic balloon pumps to maintain hemodynamics.

Table 8
Baseline Hemodynamics – Core Implant Patients

Hemodynamic Measurement	Mean Value (SD) n = 81
Cardiac Index (L/min/M²)	1.9 (0.5) n = 65
Cardiac Output (L/min)	3.9 (1.1) n = 65
Systemic Vascular Resistance (dyne-sec/cm^5)	1108.9 (393.7) n = 68
Pulmonary Vascular Resistance (dyne-sec/cm^5)	221.7 (116.8) n = 78
Heart Rate (bpm)	101.3 (20.7) n = 81
Systolic Arterial Pressure (mm Hg)	92.8 (15.2) n = 79
Mean Arterial Pressure (mm Hg)	68.1 (9.1) n = 79
Pulmonary Artery Systolic Pressure (mm Hg)	55.2 (13.5) n = 72
Pulmonary Artery Mean Pressure (mm Hg)	41.1 (10.8) n = 72
Pulmonary Capillary Wedge Pressure (mm Hg)	29.6 (10.6) n = 68
Central Venous Pressure (mm Hg)	19.7 (6.9) n = 77
Organ Perfusion Pressure (mm Hg)	48.6 (10.9) n = 75

Table 9
Baseline Blood Chemistry and Hematology
Core Implant Patients

Chemistry/Hematology Measurement	Mean Value (SD) n = 81
Chemistry	
Sodium (mEq/L)	132.0 (6.7) n = 79
Potassium (mEq/L)	4.4 (0.9) n = 80
Chloride (mEq/L)	96.1 (6.7) n = 79
Blood Urea Nitrogen (mg/dL)	36.2 (18.7) n = 79
Creatinine (mg/dL)	1.7 (0.6) n = 81
Total Bilirubin (mg/dL)	2.0 (1.3) n = 79
SGOT (IU/L)	189.9 (773.1) n = 77
Hematology	
White Blood Cell Count ($10^3/\mu L$)	11.4 (4.1) n = 80
Red Blood Cell Count ($10^6/\mu L$)	3.8 (0.7) n = 80
Hematocrit (%)	33.7 (6.1) n = 80
Platelet Count ($10^3/\mu L$)	213.0 (93.6) n = 77
Plasma Free Hemoglobin (mg/dL)	11.5 (16.0) n = 64
Coagulation Panel/Cytotoxicity	
Prothrombin Time (sec)	16.4 (4.4) n = 79
International Normalization Ratio (INR)	2.0 (1.5) n = 79
Partial Thromboplastin Time (sec)	37.3 (12.7) n = 75
Fibrinogen (mg/dL)	467.4 (198.6) n = 62
Cytotoxic Antibody (%)	0.0 (0.3) n = 76

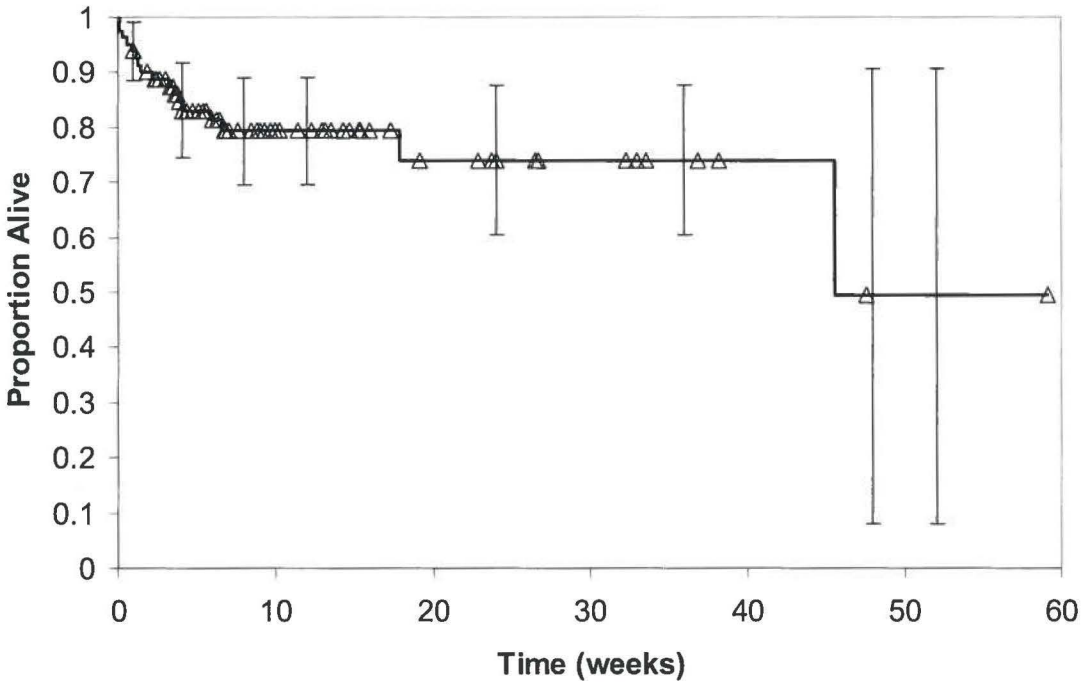
The mean core patient wait for a donor heart was 79 days, with a median wait time of 47 days.

Table 10 Time to Transplant or Death

Time	Statistic	Core n = 81
Duration (days)	Mean (SD)	79.1 (83.9)
	Median	47.0
	Min-Max	1.0 - 414.0
Total Duration (days)		6411

Figure 1 graphically shows the estimate of survival to transplant or death for the core implant group by time.

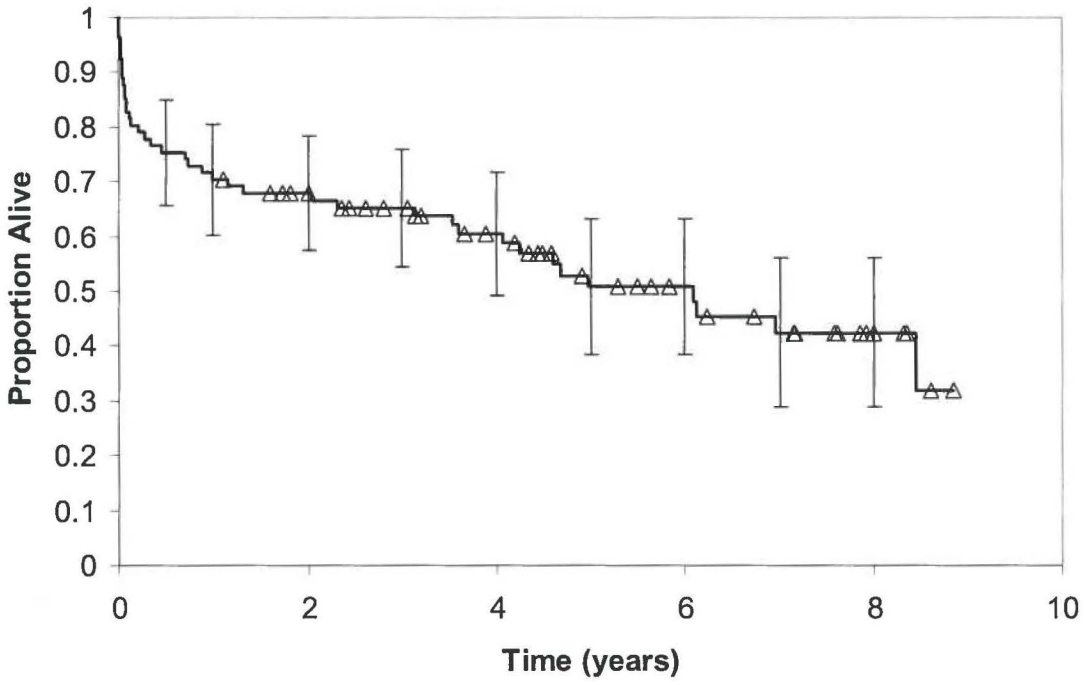
Figure 1 – Kaplan-Meier Estimate of Duration of Survival to Transplant or Death (Core Patients)



Time (weeks)								
	1	4	8	12	24	36	48	52
Core (n=81)								
Survival rate (%)	93.8	83.1	79.3	79.3	74.0	74.0	49.4	49.4
Standard error (%)	2.7	4.3	4.9	4.9	6.8	6.8	20.7	20.7
n	75	55	37	26	10	5	1	1

All patients in this study reached at least the 2 year post transplant interval and at 2 years the survival was 68%.

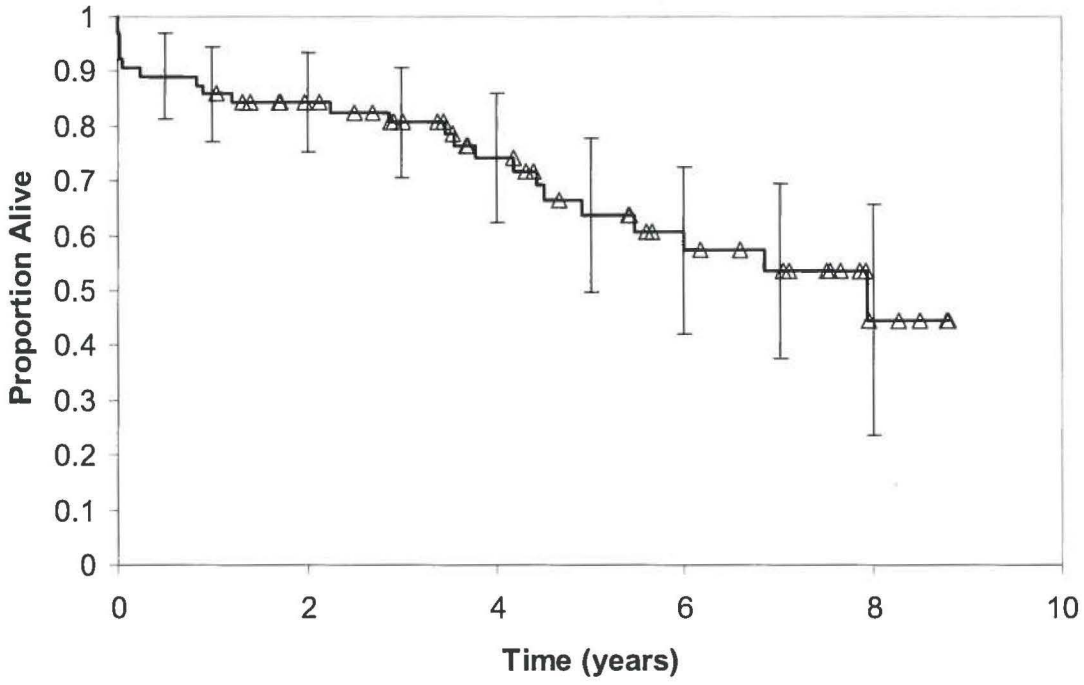
Figure 2 – Kaplan-Meier Estimate of Overall Duration of Survival (Core Patients)



Time (years)								
	0.5	1	2	3	4	5	6	7
Core (n=81)								
Survival rate (%)	75.3	70.4	67.9	65.1	60.4	50.8	50.8	42.4
Standard error (%)	4.8	5.1	5.2	5.3	5.6	6.2	6.2	6.8
n	61	57	51	44	35	24	19	14

Survival post transplant was comparable between the core patients and published survival of all cardiac recipients on the UNOS list. Sixty four of 81 core patients received transplants, with a post transplant survival rate at 1 year of 85.9% (vs. 84.7% UNOS), and a 5 year survival rate of 63.8% (vs. 69.8% UNOS).

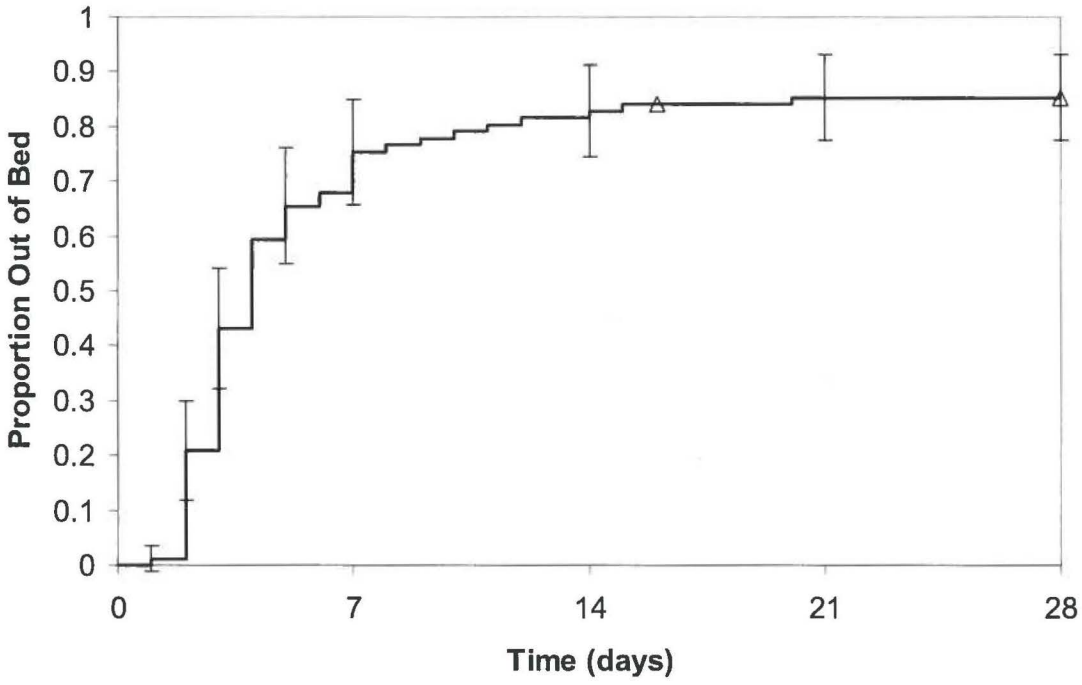
Figure 3 – Kaplan-Meier Estimate of Duration of Survival from Transplant (Core Patients)



Time (years)								
	0.5	1	2	3	4	5	6	7
Core (n=64)								
Survival rate (%)	89.1	85.9	84.3	80.7	74.1	63.8	57.4	53.5
Standard error (%)	3.9	4.3	4.5	5.0	5.9	7.0	7.6	8.0
n	57	55	48	41	32	23	17	14

The core TAH-t patients' ability to get out of bed and ability to walk over 100 feet was significantly improved. Approximately 65% of the core patients were out of bed by the 5th day after implant. Two weeks after implant, 60% of core patients were walking over 100 feet.

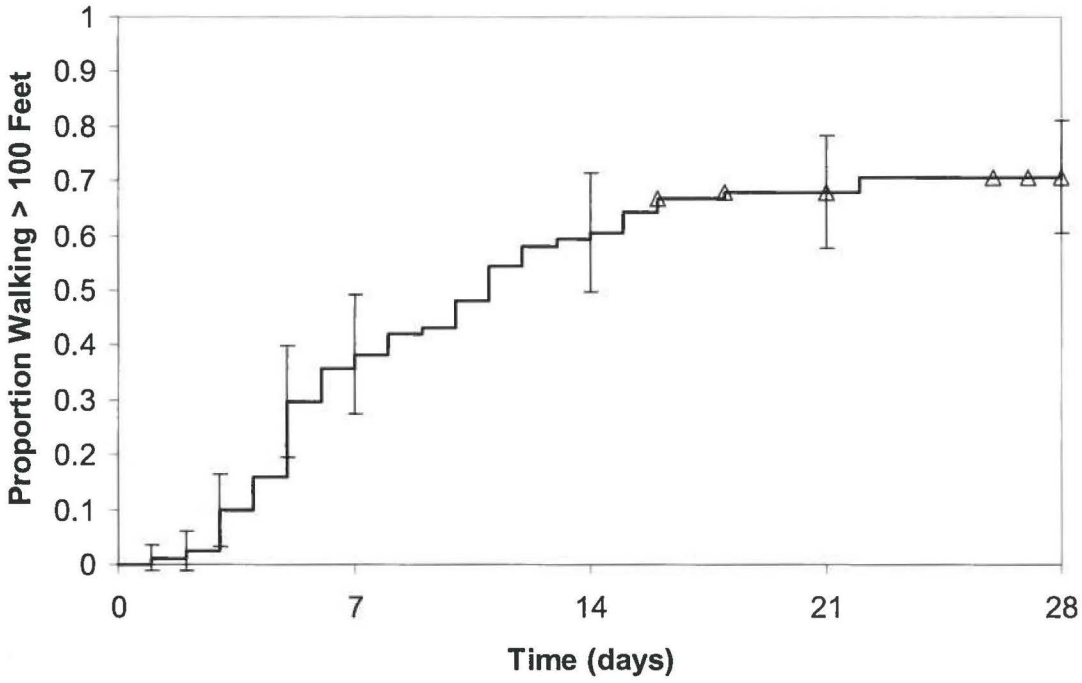
Figure 4 – Kaplan-Meier Estimate of Time to First Getting Out of Bed (Core Patients)



Time (days)								
	1	2	3	5	7	14	21	28
Core (n=81)								
% walking	1.2	21.0	43.2	65.4	75.3	82.7	85.3	85.3
Standard error (%)	1.2	4.5	5.5	5.3	4.8	4.2	4.0	4.0
n	80	64	46	28	20	14	11	11

Note: *Time to getting out of bed is the number of days from enrollment/implant to first getting out of bed or transplant. Patients who die before getting out of bed are censored at 9999 days; patients transplanted before getting out of bed are censored at day of transplant.*

Figure 5 – Kaplan-Meier Estimate of Time to First Walking > 100 Feet (Core Patients)



Time (days)								
	1	2	3	5	7	14	21	28
Core (n=81)								
% walking > 100 ft	1.2	2.5	9.9	29.6	38.3	60.5	67.9	70.7
Standard error (%)	1.2	1.7	3.3	5.1	5.4	5.4	5.2	5.1
n	80	79	73	57	50	32	23	19

Note: *Time to walking>100 ft is the number of days from enrollment/implant to first walking > 100 ft or transplant. Patients who die before walking >100 ft are censored at 9999 days; patient transplanted before walking >100 ft are censored at the day of transplant.*

Core patients had an immediate and sustained improvement in their hemodynamic variables while on the TAH-t awaiting transplantation. Cardiac index improved from 1.9 L/min/m² to 3.0 L/min/m² immediately after implant, a 58% improvement, with sustained levels throughout the implant period. Systolic blood pressure increased from a baseline 92.8 mm Hg to 122.7 mm Hg, a 32% improvement, immediately following transplant, and was also sustained through the implant period.

Organ perfusion pressure (transcapillary or whole body perfusion pressure) increased by 42% immediately following implant with the TAH-t. An increase in perfusion pressure is a measurement of increased whole-body perfusion which leads to organ recovery. Perfusion pressure is calculated by subtracting the central venous pressure from the mean arterial pressure. Perfusion pressure was improved and maintained throughout the implant period for core implant patients.

Figure 6 – Mean (+/- 2SE) Cardiac Index by Study Period (Core Patients)

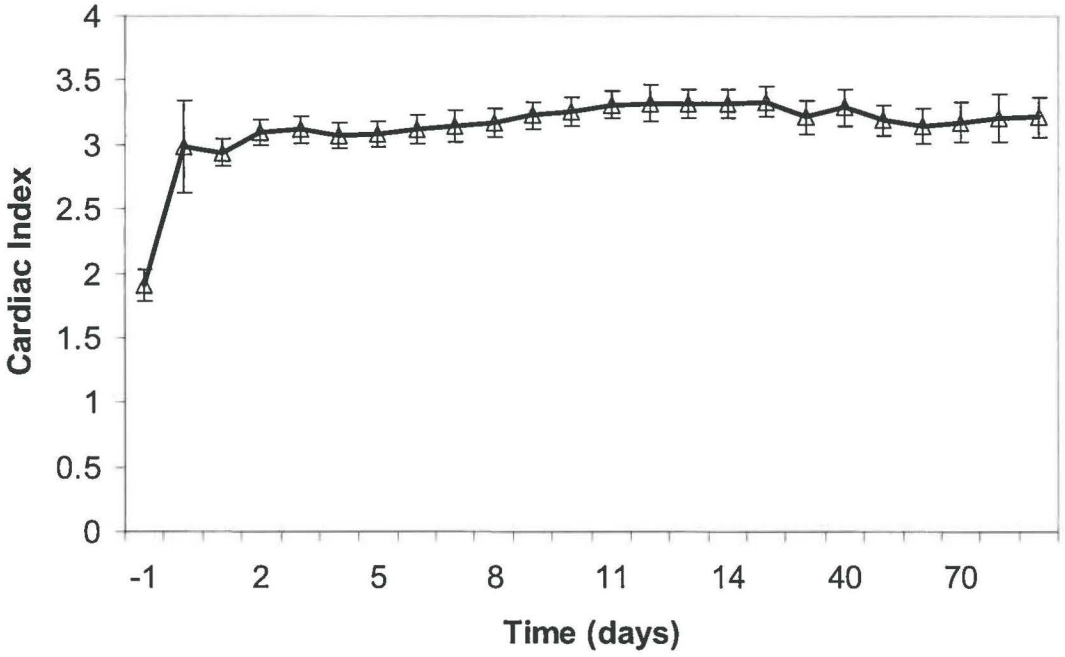


Figure 7 – Mean (+/- 2SE) Systolic Arterial Pressure by Study Period (Core Patients)

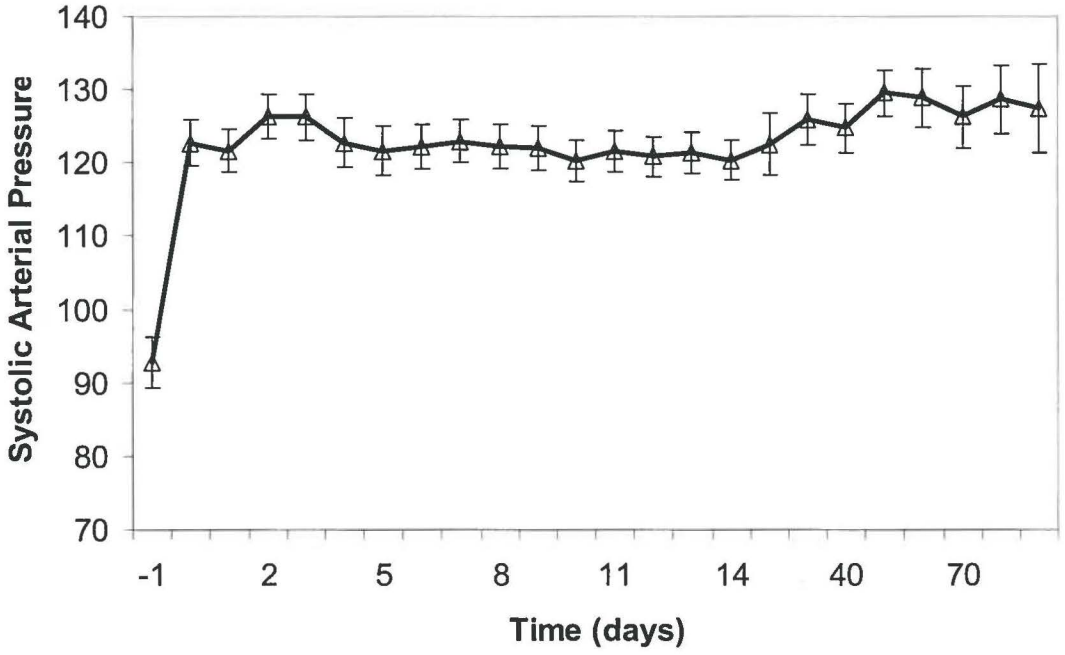
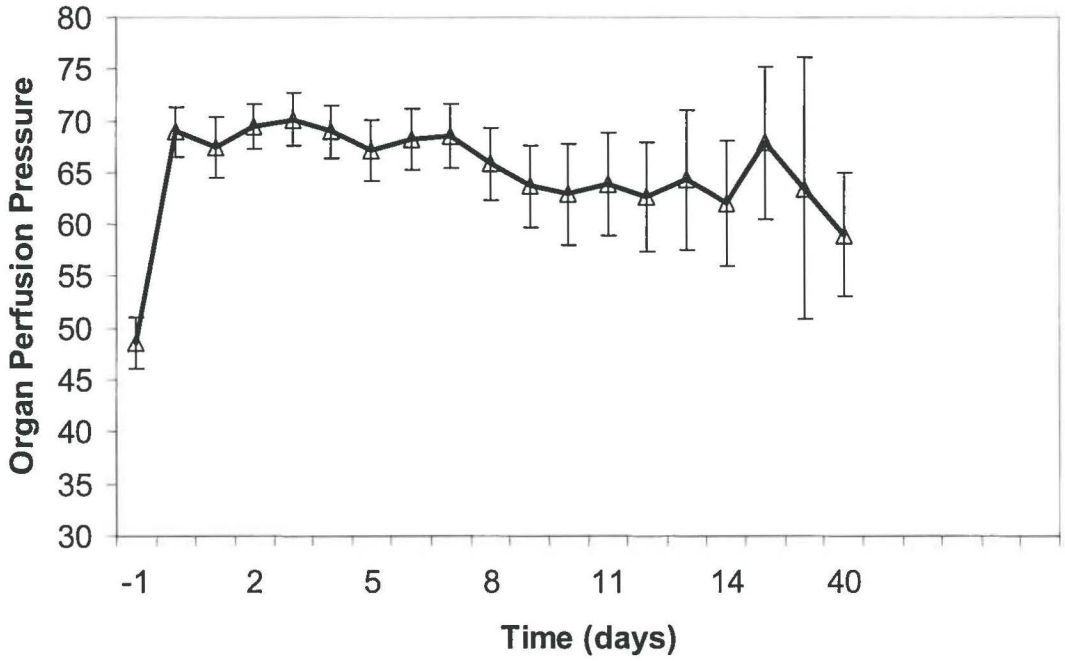


Figure 8 – Mean (+/- 2SE) Organ Perfusion Pressure by Study Period (Core Patients)



Both renal and hepatic function in the core implant population normalized after 3 weeks. At study entry the renal and hepatic functions were adversely affected by the patients' heart conditions shown by elevated blood urea nitrogen (BUN), creatinine, total bilirubin and SGOT levels above maximum normal. After the TAH-t implant surgery and recovery from surgery (approximately 3 weeks) the levels normalized in the core group and were often in the normal range for these markers of renal and hepatic function.

Figure 9 – Mean (+/- 2SE) BUN by Study Period (Core Patients)

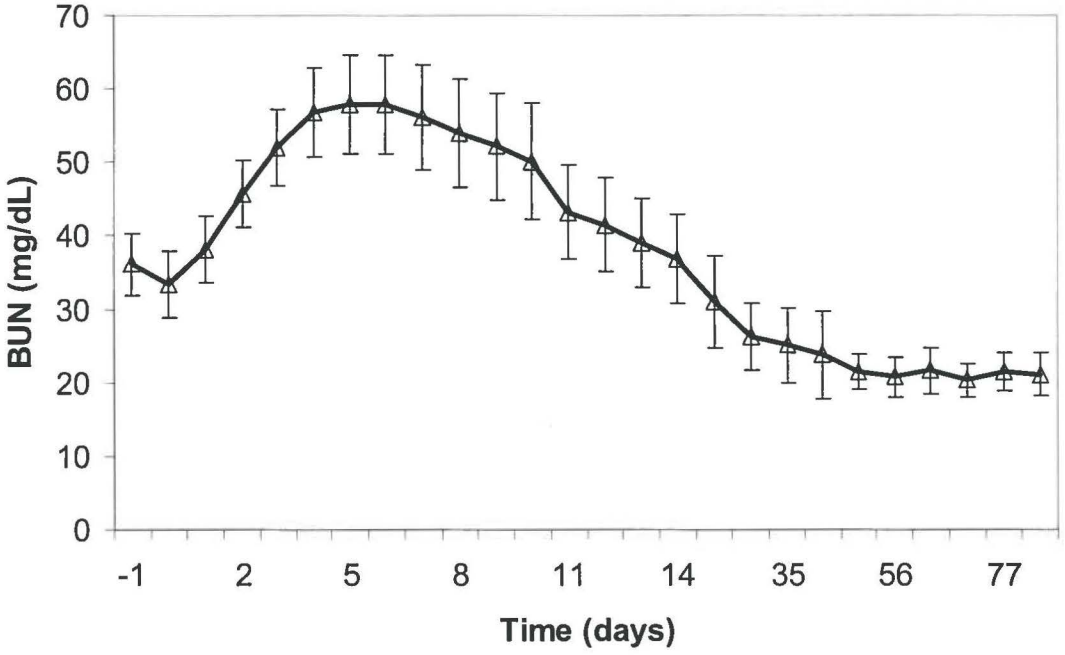


Figure 10 – Mean (+/- 2SE) Creatinine by Study Period (Core Patients)

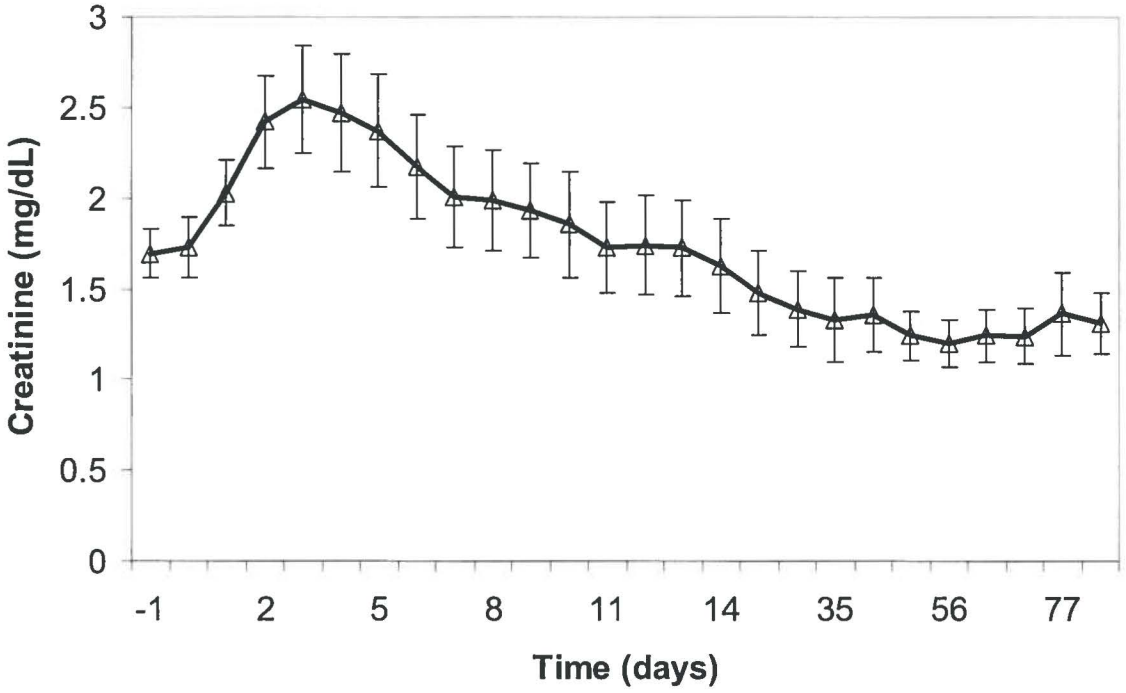


Figure 11 – Mean (+/- 2SE) Total Bilirubin by Study Period (Core Patients)

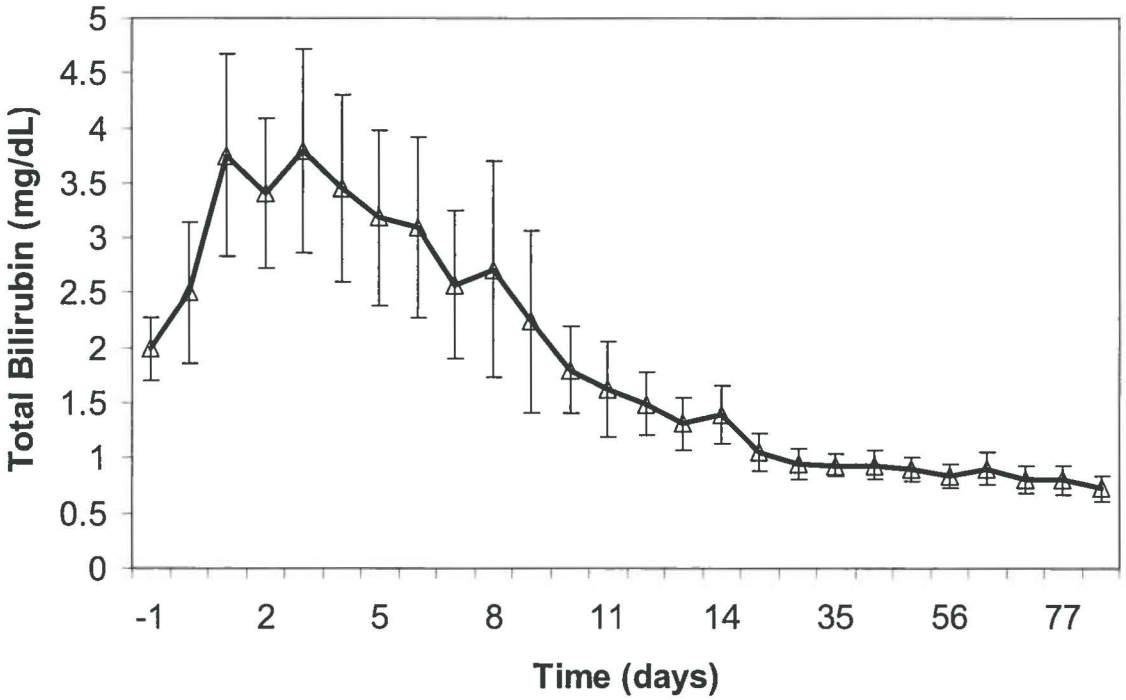
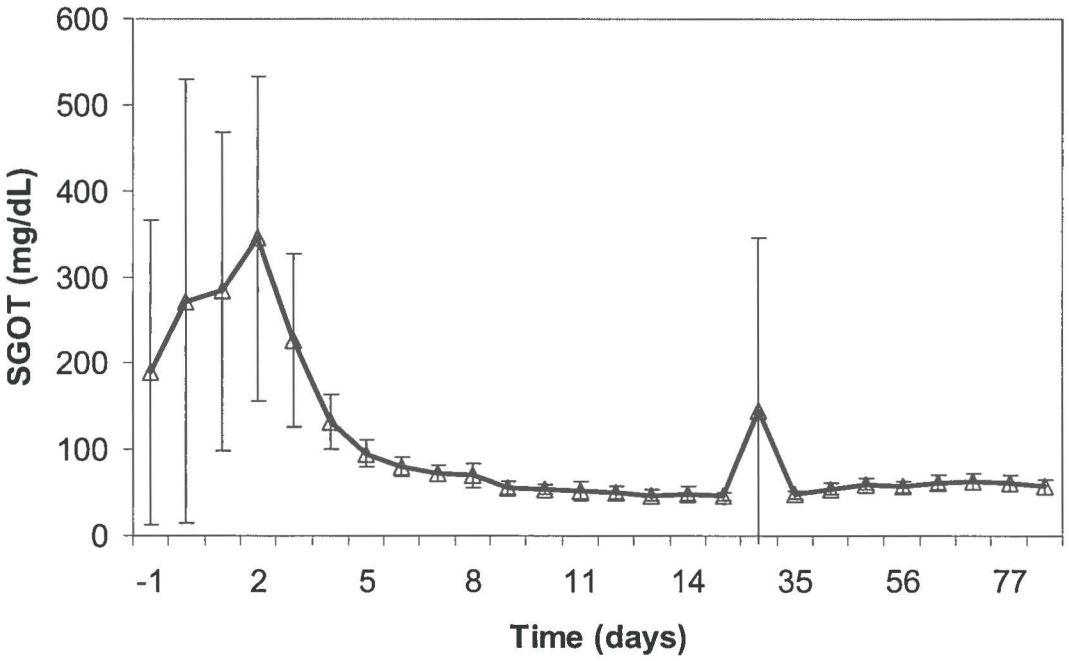


Figure 12 – Mean (+/- 2SE) SGOT by Study Period (Core Patients)



F. Results

The primary endpoint of the study was treatment success. To be considered a success the patient must have been, at 30-days post transplantation: 1) alive; 2) NYHA Class I or II; 3) ambulatory; 4) not ventilator dependent; and 5) not on dialysis. Patients who failed these criteria were considered failures with respect to the study. At 30 days post transplant, 69.1% (56/81) of the core implant group met the criteria for treatment success.

Table 11- Clinical Trial Outcomes - Core Patients

Outcome n(%)a (95% CI)	Core Patients N=81
Survived to transplant	64 (79.0%) (68.5% - 87.3%)
Survived to 30 days post Transplant	58 (71.6%) (60.5% - 81.1%)
Treatment success (30 days post Transplant)	56 (69.1%) (57.9% - 78.9%)

Device effectiveness results establish that the SynCardia CardioWest temporary Total Artificial Heart is effective in providing bridge to transplant circulatory support in cardiac transplant candidates at risk of imminent death from biventricular failure. Secondary effectiveness parameters measured the improvement in hemodynamics, the ability to ambulate and to walk 100 feet for core patients awaiting transplant. At the time of TAH-t implantation, cardiac index increased to an average of 3.0 l/min/m^2, an increase of 58% from baseline. Following TAH-t implant, systolic blood pressure increased to an average of 123 mm Hg (32% from baseline), and mean transcapillary perfusion pressure (mean blood pressure minus central venous pressure) increased to an average of 69 mm Hg, up 42% from baseline, an indication of improved organ perfusion. This near normalization of hemodynamic parameters corresponded to the ability of core patients to ambulate and walk more than 100 feet. By two weeks 71.6% of core patients were ambulatory, and 60.5% could walk >100 feet.

Both renal and hepatic recovery with normal laboratory parameters was evident within one month after implant of the TAH-t.

XI. CONCLUSIONS

Results demonstrate that the SynCardia CardioWest temporary Total Artificial Heart performed reliably on the bench and as intended during the clinical trial. The materials used in its composition are biocompatible with human tissue and blood. The device meets the FDA and ISO guidelines to assure sterility.

All patients enrolled in the study had the opportunity to reach at least 24 months follow-up. Outcomes are summarized in the table below.

Table 12
Summary of Outcomes

Outcome	Core
Overall Survival	
Survival overall at 6 months	75.3%
Survival overall at 12 months	70.4%
Survival overall at 24 months	67.9%
Survival to Transplant	
Survival to transplant	79.0%
Time to Transplant	
Mean time to Transplant or death	79.1 days
Eligibility for Transplant	
Hepatic function normalization	21 days
Renal function normalization	28 days
Mean Organ Perfusion (day 1) increase from baseline	Δ 21.1 mm Hg
Quality of Life While Awaiting Transplant	
Cardiac index (day 1) increase from baseline	Δ 1.1 L/min/m^2
% patients ambulatory	86.4%
% patients walking 100 feet	75.3%
Overall Treatment Success	
Alive 30-days post Tx, NYHA Class I or II, and not bedridden, ventilator dependent or on dialysis	69.1%

The clinical study showed that the device is effective as a bridge-to-transplantation in patients who are at imminent risk of dying from biventricular heart failure. The data obtained in this trial demonstrate that the CardioWest temporary Total Artificial Heart is effective support for patients waiting for donor hearts. In patients implanted with the TAH-t, hemodynamic status improved and renal and hepatic function returned to normal within one month. Treatment outcomes post transplant were nearly identical for the core patients compared to all UNOS patients.

The benefits offered to the patients implanted with the SynCardia TAH-t include the additional time to await transplant and, improved hemodynamics resulting in early ambulation. These benefits outweigh the risks associated with adverse events that occurred.

XII. PANEL RECOMMENDATIONS

At an advisory panel meeting held on March 17, 2004, the Circulatory System Devices Panel recommended that the SynCardia System's PMA for the SynCardia Systems, Inc. CardioWest temporary Total Artificial Heart (TAH-t) be approved subject to submission to, and approval by, the Center for Devices and Radiological Health (CDRH) to the following:

1. A year long postmarket study and adding a contraindication that the device should not be used in patient in whom it would not fit.

2. A contraindication for patients who cannot receive anticoagulation therapy.

3. A warning that safety was not assessed in those patients who are not candidates for anti-platelet therapy.

4. Surgeons be required to view a human transplant with the device before attempting their own procedure.

XIII. CDRH DECISION

CDRH concurred with the Panel recommendation of March 17, 2004, and issued a letter to SynCardia Systems, on April 9, 2004, advising that its PMA was approvable subject to SynCardia Systems modifying the Instructions for Use and Summary of Safety and Effectiveness and also agreeing to the conditions of approval as recommended by the Panel and required by FDA. A postapproval study was necessary to provide assurance that the success of the device at one center can be reproduced at different centers. A postapproval study protocol detailing the number of patients (at least 50) that will be followed, the duration of follow-up (at least 1 year), and the endpoints (including, but not necessarily limited to survival to transplant, adverse events, device malfunction, etc) was requested. In an amendment received by FDA on August 16, 2004, SynCardia Systems submitted the

required data regarding their agreement to the postapproval study and Instructions for Use modifications. It should be noted that the postapproval protocol will be submitted as a supplement to the PMA once approval is obtained.

FDA issued an approval order on October 15, 2004. The applicant's manufacturing facility was inspected on January 7, 8, 9, 12 and 13, 2004 and September 21, 22 and 23, 2004, and was found to be in compliance with the Quality System Regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATION

Directions for use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.

TAB 5

SynCardia Systems, LLC
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United States SynCardia TAH-t Certified Centers

Center
UMC-University of Arizona Medical Center, Tucson
Cleveland Clinic Foundation
MCV-VCU
Ohio State University, Ross Heart Hospital
Aurora St. Luke's Medical Center, Wis
University of Michigan Ann Arbor Transplant Center
Barnes-Jewish Hospital
Hospital University of Pennsylvania (HUP)
Penn State Hershey Medical Center
University of Maryland Medical Center
Mayo Clinic, Phoenix AZ
Intermountain Medical Center (formerly LDS Hospital, SLC)
Integris Baptist Medical Center-Oklahoma
Methodist Hospital
UCSD Medical Center
Texas Children's Hospital
USC Keck Hospital
University of Iowa
Columbia University Medical Center-NY Presbyterian Hospital
Texas Heart Institute
Sacred Heart Medical Center/Providence Healthcare
Sentara Norfolk General Hospital
University of Chicago
Cedars-Sinai Medical Center
University of Washington
Children's Hospital of Philadelphia
University of Kentucky
Allegheny General Hospital
Brigham & Women's Hospital
Mayo Clinic, Rochester MN
Phoenix Children's Hospital
Jewish Hospital & St.Mary's at University of Louisville
Strong Memorial Hospital/University of Rochester Medical Center
Advocate Christ Medical Center
Mount Sinai Medical Center
Memorial Hermann Healthcare
UCLA Medical Center

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Center
Children's Hospital of Wisconsin
Cincinnati Children's Hospital
University of Utah Medical Center
Ochsner Medical Center
Nebraska Medical Center
Thomas Jefferson University
University of Minnesota Medical Center/Fairview Health
Shands Hospital at U of Florida
Inova Fairfax Hospital
Stanford University School
Indiana University Health (Formerly Methodist Indianapolis)
Baylor University Medical Center
St. Vincent Hospital-Indianapolis
Children's Medical Center Dallas
Carolinas Medical Center
Temple University Hospital
Abbott Northwestern Hospital/Allina Hospitals (formerly Minneapolis Heart Institute)
Henry Ford Hospital
Duke University Hospital
Tampa General Hospital
University of Virginia Medical Center
Lurie Children's Hospital of Chicago
University of Alabama
Baptist Health-BMC Baptist Cardio Institute
Florida Hospital
Froedtert Memorial Hospital
Seattle Children's Hospital
Banner Good Samaritan MC
Arkansas Children's Hospital
Vanderbilt
Saint Thomas West Hospital-Nashville