The 50/50 cc Total Artificial Heart Trial: Extending the Benefits of the Total Artificial Heart to Underserved Populations

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While use of the total artificial heart (TAH) is growing, the use of the device is not uniform across the gender and age spectrum because the vast majority of implants are in adult males. SynCardia has recently developed a smaller 50 cc TAH that was designed to accommodate patients with a body surface area as low as 1.2 m^2 (potentially even lower using virtual implantation). Herein, we describe the early use of the 50 cc TAH (10 implants in the US and 18 outside the US). Twenty-eight devices have been implanted worldwide. Nineteen (68%) patients were female, 4 (14%) were 21 years of age or younger, and 2 (7%) had a diagnosis of congenital heart disease (1 Fontan). The smallest patient, by body surface area, was 1.35 m^2. Six patients (21%) have been placed on the Freedom Driver, all of whom have survived. Fourteen patients (50%) have had a positive outcome to date. The development of the 50 cc TAH has expanded the population of patients who may benefit from TAH support and thus may help improve outcomes for patients who have had limited biventricular support options to date.
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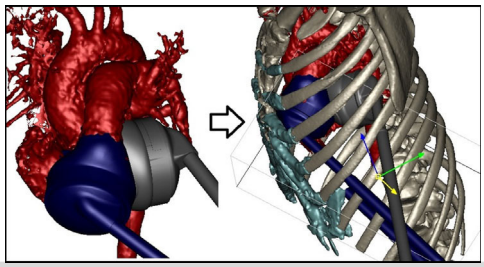
Introduction

The total artificial heart (TAH) was developed for use in adults with end-stage heart disease and biventricular heart failure or a contraindication to left ventricular assist device (LVAD).[1] This includes patients with congenital heart disease with multiple residual lesions, failing right ventricle in the setting of existing LVAD, intractable arrhythmias, cardiac tumors, heart transplant graft failure (allows for discontinuation of immunosuppression), active malignancy receiving cardiotoxic therapies, restrictive disease, or unresectable blood clot. A total of 1596 implantations have occurred worldwide as of May 11, 2016, approximately 45% of which were implanted between 2010 and 2015 (personal communication, SyCcardia, May 2016). While use of the TAH is growing, use of the device is not uniform across the gender and age spectrum because the vast majority of the implants are in adult males with dilated cardiomyopathy. Only 12% of all TAH implantations (198) have been implanted in women and even less, 5% (75), have been implanted in pediatric patients (largely because of concerns regarding fit of the device). This mimics the case



Virtual fit testing of 50/50 cc Total Artificial Heart (TAH) within a patient's chest wall.

Central Message

The 50 cc SynCardia Total Artificial Heart (TAH) has expanded the support options available to smaller and younger patients in need of biventricular support.

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with ventricular assist devices (VADs), where approximately 80% of device implantations have been in adult males.[2,3] This disparity is driven in part by patient size. Historically, the 70 cc TAH was only considered for patients with a body surface area (BSA) $\geq$ 1.7 m^2 and an anteroposterior distance from the sternum to the 10th thoracic vertebra of at least 10 cm^1. Virtual implantation has expanded these criteria.[4] However, patient size remains a limiting factor to broader use of the TAH in smaller patients, including women (small men), children, and patients with congenital heart disease.

SynCardia Systems (Tucson, AZ) has recently developed a new, smaller 50 cc TAH that was designed to accommodate patients with a BSA as low as 1.2 m^2 (potentially even lower using virtual implantation). The device is essentially the same device as the 70 cc SynCardia TAH, with the exception of the 29% reduction in size. It has two 50 cc ventricles and a 25 mm inflow valve and 23 mm outflow valve compared with the 70 cc ventricles and the 27 and 25 mm valves in its predecessor. The valves remain SynHall valves, though they are now manufactured by SynCardia (approved by the FDA in 2014). The 50 cc SynCardia (Tuscon, Arizona) is compatible with the Freedom Driver, although some of the current alarms for the driver have not yet been calibrated for the smaller volume model. The development of this device should allow the device to be implanted in women and children, in particular the growing group of adolescents with palliated congenital heart disease. Herein we describe the early use and outcomes of the 50 cc TAH and the ongoing 50 cc Bridge to Transplant FDA study.

50 cc TAH Clinical Study

SynCardia is currently conducting an Investigational Device Exemption study of the 50 cc TAH as a bridge to transplant in the US, which opened enrollment in October 2015. This is a non-randomized, prospective, multicenter study that features three arms: (1) a pediatric arm, ages 10 to 18 years; (2) an adult arm, ages 19 to 75 years; and (3) a secondary arm (a compassionate use arm). The pediatric arm will evaluate the safety and probable benefit of the 50 cc TAH to support a Humanitarian Device Exemption application, while the adult arm will evaluate the safety and efficacy of the device to support a Premarket application.

Goal enrollment in the pediatric and adult arm is 24 patients each. There are 30 sites participating in enrollment in the pediatric arm and 40 sites participating in enrollment in the adult arm.

Inclusion criteria are as follows:

1) Eligible for cardiac transplant
2) At imminent risk of death from biventricular heart failure
3) Age 10 to 18 years for the pediatric arm, or age 19 to 75 years for the adult arm
4) Two functional atrioventricular valves
5) BSA of 1.2 m^2 to 1.85 m^2 and adequate sternum to T10 distance or adequate room in the chest for implantation as determined by virtual implantation evaluation.

Exclusion criteria are as follows:

1) Insufficient space in the chest by virtual implantation evaluation
2) Patient cannot be adequately anticoagulated on the TAH
3) Extracorporeal membrane oxygenation support $>$ 3 days at the time of proposed implant
4) Current support with an investigational device
5) Greater than 30 minutes of CPR within 14 days of proposed implant
6) Stroke within 30 days of proposed implant
7) Dialysis dependent at time of proposed implant.

The primary endpoint will be to assess if the 50 cc TAH can safely support patients with biventricular heart failure. The following will be assessed at 6 months post-implant (and with continuing follow-up for those supported for $>$ 6 months):

1) Bridge to transplantation
2) Alive on support at 6 months without permanent, disabling stroke
3) Death.

Safety will be assessed via the characterization of the following adverse events (all as defined by Interagency Registry For Mechanical Circulatory Support [INTERMACS] definitions):

1) Incidence of major infection/sepsis
2) Neurologic events/stroke
3) Chronic renal dysfunction
4) Rate of major device failure.

Of note, this study will be the first FDA study that will include the virtual implantation evaluation as a criterion for patient selection. Historically, use of the 70 cc TAH was limited to patients with a BSA of 1.7 m^2 and an anteroposterior distance from the sternum to the 10th thoracic vertebra of at least 10 cm.[5] These size recommendations were made to prevent vascular compression (especially the inferior vena cava and the left pulmonary veins). These size recommendations have been augmented by personalized device fitting using virtual implantation. The clinical use of this technology has been described for both the 50 cc and 70 cc TAH and will likely continue the shift to an individualized approach for device placement.[4,6] This is especially relevant in the case of pediatric and adolescent patients who have a more diverse group of heart failure etiologies and anatomy, notably congenital heart disease. The cardiac mass and chest wall shape (i.e., scoliosis, pectus excavatum) can be quite variable in these populations and may accommodate innovative placement options.[7] We are also optimistic that a combination of the smaller device footprint and virtual implantation may allow patients with a BSA smaller than 1.2 m^2 (perhaps down to 0.9 m^2) to be implanted with the device.