Xenotransplantation vs Total Artificial Heart: Which is the Future Alternative to Heart Transplantation

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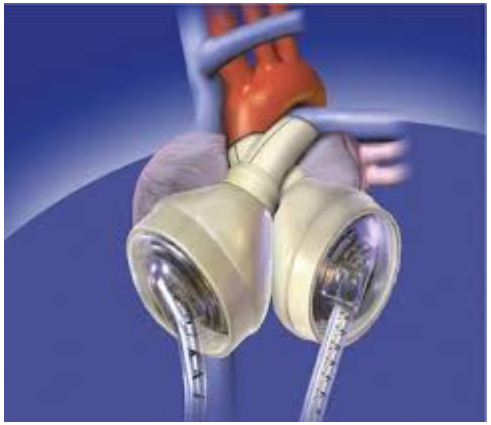
Background

- 4-5 million individuals with CHF in the US
- ~ 400,000 new cases added every year
- ~ 20% wait list mortality
- < 3000 OHTs performed in the US
- Solution:

VS



Immunologic Barriers to XenoTx

- Severe immune response to a nonprimate mammalian heart vs nonhuman primate (NHP) heart
- **Hyperacute rejection** (predominantly humoral or Ab-mediated): interaction between a CHO Ag (galactose-a1,3-galactose) expressed on the graft and sepcifics anti-Gal Abs present in the NHP blood. They are developed within a few months after birth as a response to colonization of the intestinal tract by microorganisms and viruses that express Gal
- Solution: genetically engineered pigs
- Other Ags are expressed on pig cells the nature of which is uncertain

Immunologic Barriers to XenoTx

- **Acute Cellular rejection (T cell mediated):** Conventional immunosuppressive regimens must be administered in higher dosages than are required for alloTx: associated with a high incidence of infections and other complications
- **Coagulation Dysfunction:** result from chronic activation of the graft vascular endothelium by binding of the anti-non-Gal antibody and complement fraction deposition resulting a change from normal anticoagulant state of the endothelium to a procoagulant state
- Solution: genetically engineered pigs inserting "anticoagulant" genes
- Not 100% effective and still needs other pharmacotherapy

Barriers to XenoTx

- **Inflammatory Response:** There is interaction between immune, coagulation and inflammatory responses
- **Graft Vasculopathy (Chronic Rejection):** Cause unknown but most likely 2/2 chronic graft endothelial activation
- **Complexity and high technical failure rate**
- **Ethical Challenge and Regulatory Guidelines**

Milestones need to be achieved before clinical trial

- Consistent survival of NHP recipient of an orthotopically transplanted pig heart for at least 3 months and preferably for 6 months without major complications relative to the intensity of the immunosuppressive regimen such as infection
- The availability of a facility to breed and house genetically engineered pigs protecting them from being exposed to infectious agents, including viruses, that could be transferred to the recipient
- Proving that the transfer of porcine endogenous retroviruses, that are present in the genome of every pig cell, will not be a health risk to the recipient, hos/her family, medical staff and community
- The need for a pig that does not express oligosaccharide N-glycolylneuraminic acid (NeuGc) since humans do make anti-NeuGC Abs vs NHPs
- Will immune response to the xenograft, used as a bridge to allotx, sensitize the recipient to a subsequent allograft?????

Indications of XenoTx

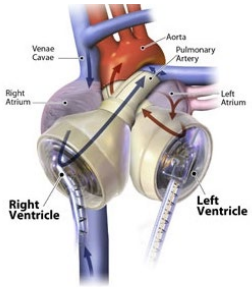
- ? Retransplant candidates
- ? Highly sensitized patients
- ? Contraindications to MCS

Total Artificial Heart

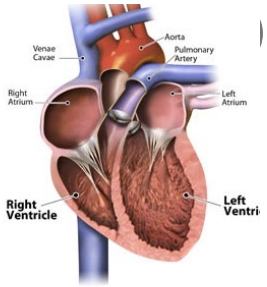
- 1981: FDA approved the investigational use of Jarvik-7 (Utah Heart)
- 1985: Copeland showed the utility of Jarvik-7 for BTT
- 1990: FDA stopped production of Jarvik-7 2/2 quality assurance and reporting failures by Symbion Inc (Salt Lake City, UT)
- 1992: CardioWest Technologies in Tucson obtained FDA approval for limited manufacture of Jarvik-7 for BTT; acquired assets and technologies from Symbion
- 2001: SynCardia Systems was incorporated to manufacture the CardioWest TAH

Total Artificial Heart

- Two sperate blood pumps pneumatically driven and generate pulsatile flow
- 70cc and 50cc pump
- 4 mechanical valves
- External source of compressed air by a wire-reir
- Portable driver for ease and discharge

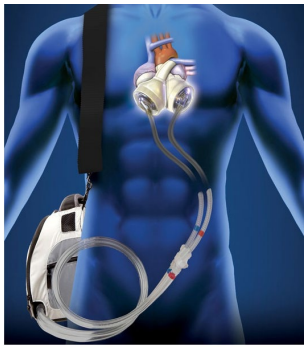


Total Artificial Heart



Human Heart


1A. SynCardia 70cc and 50cc TAHs



INTERMACS Profile Pre TAH Implant

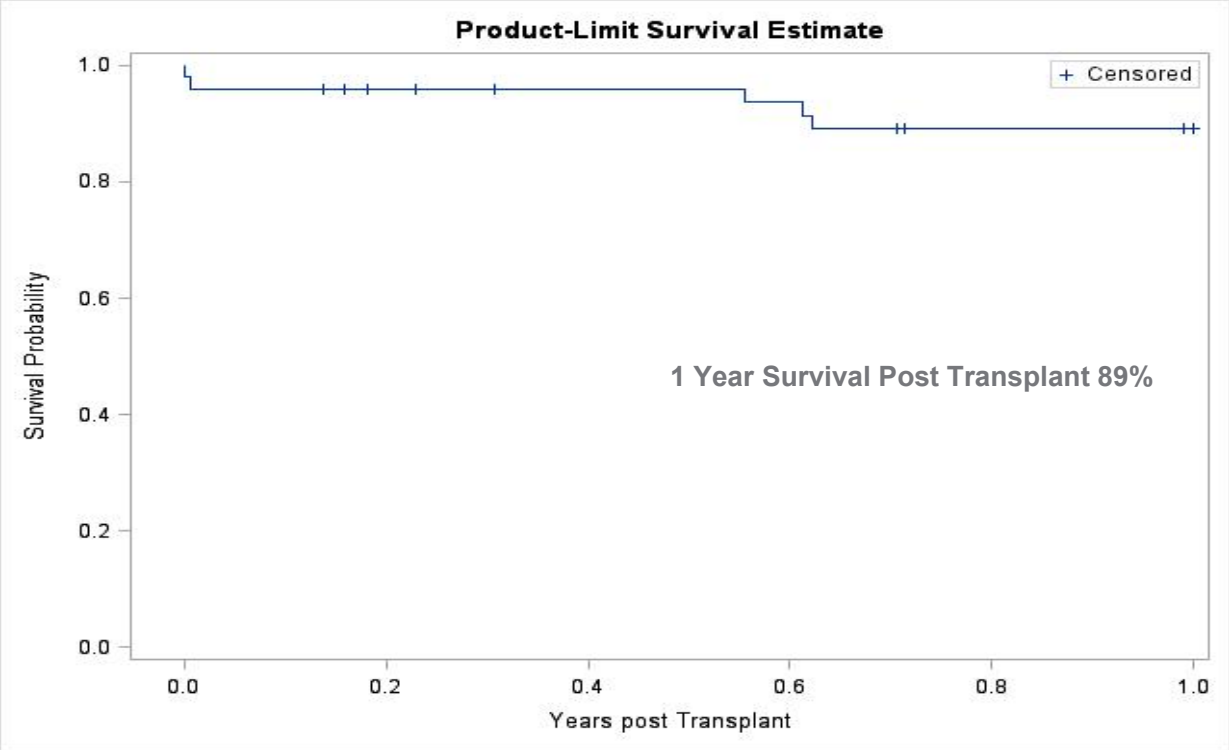
Intermacs Profile Category , n(%)	
Intermacs 1	51 (53.1)
Intermacs 2	29 (30.2)
Intermacs 3	8 (8.3)
Intermacs >=4	8 (8.3)

Adverse Events in the First Year Post TAH Implant

Major Bleeding, n(%)	Stroke, n(%)	Infection, n(%)
38 (39.6%)	27 (28.1%)	15 (16%)

** Total number of Implants = 96

1 Year Survival Post Transplant



CARMAT TAH

A bioprosthetic total artificial heart for end-stage heart failure: Results from a pilot study

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BACKGROUND: The electro-hydraulically actuated Carmat total artificial heart (C-TAH) is designed to replace the heart in patients with end-stage heart failure, either as bridge to transplant or destination therapy. It provides pulsatile flow and contains bio-prosthetic blood contacting materials. A clinical feasibility study was conducted to evaluate the C-TAH safety and performance.

METHODS: Hospitalized patients, at imminent risk of death from irreversible biventricular failure despite optimal medical management, and not eligible for transplant or eligible but on extracorporeal life support, were enrolled. The primary endpoint was 30-days survival.

RESULTS: Four patients were implanted with the C-TAH, three as destination therapy (ages 76, 68, 74) and one as bridge to transplant (age 58). They had implant times of 74, 270, 254 and 20 days respectively. All patients were free from hemolysis, clinical neurologic events, clinical evidence of thrombus and device-related infections. Hemodynamic and physical recovery allowed two patients to be discharged home for a cumulative duration of 7 months. The anticoagulation management strategy comprised initial unfractionated heparin, from postoperative day 2, followed by low molecular weight heparin and aspirin. An increased D-dimer level was observed in all patients during months 1 to 4. Temporary suspension of heparin anticoagulation resulted in thrombocytopenia and increased fibrin monomer, reversed by resuming anticoagulation with heparin. Causes of death were device-related (2 cases), respiratory failure and multi-organ failure.

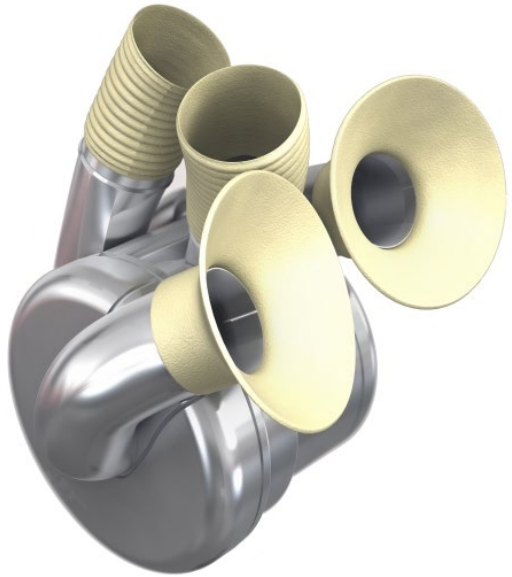
CONCLUSIONS: Preliminary clinical results with the C-TAH demonstrated good safety and performance profiles in patients suffering from biventricular failure, which need to be confirmed in a pivotal study.

J Heart Lung Transplant 2018;37:33–37

BiVACOR

Magnetically levitated rotor located between opposing pump casings. The left and right impeller blades which are mounted on either side of the rotating hub, are the key features that enables this device to support both the left and right sides of the heart.

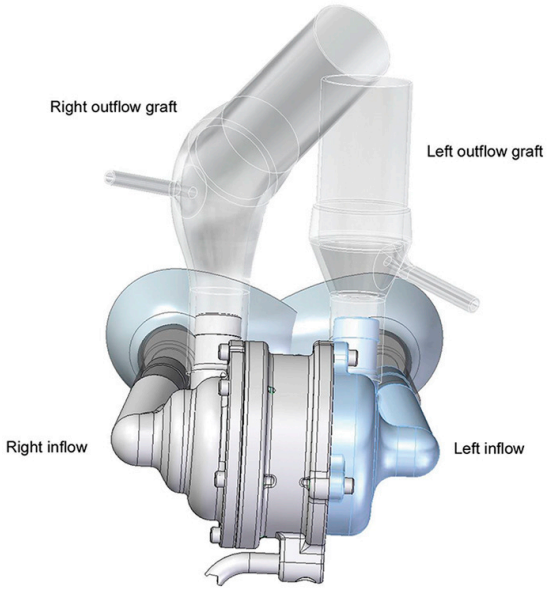
Special large gaps within the pump reduce blood cell damage and the risk of clotting

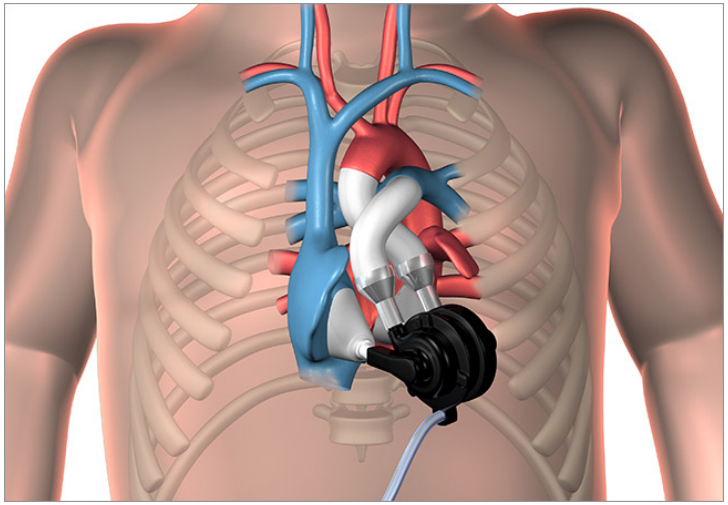


CF-TAH

Continuous-flow total artificial heart: compact, single-piece, valveless pulsatile pump providing self-regulated hemodynamic output to left/right circulation

No anticoagulation for 90 days in animal model





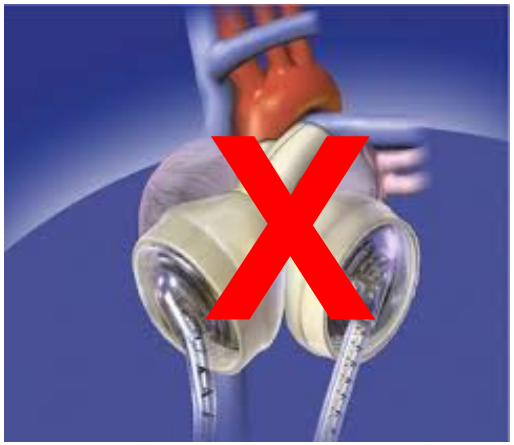
VS

1 year survival > 90%

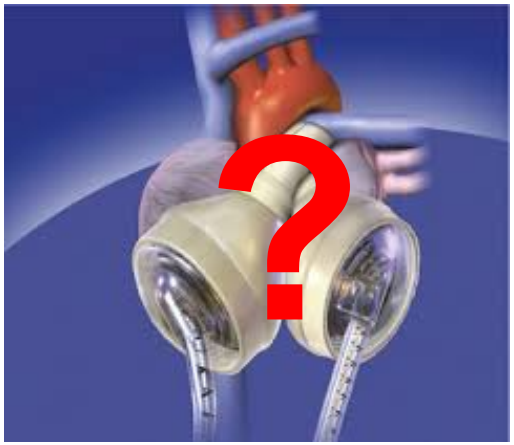
5 year survival > 75%

10 year survival > 50%

2019



2029



THANK YOU!