Total Artificial Heart as Bridge to Cardiac Retransplantation

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Mechanical circulatory support has been performed as a bridge to cardiac retransplantation in selected patients with graft failure. However, there is limited published experience on the use and potential benefit of the total artificial heart (TAH) as a bridge to cardiac retransplantation. We report on our institutional experience with 3 patients that received TAH as a bridge to retransplant, with 1 patient surviving post-retransplantation. This case series demonstrates the high-risk nature of this undertaking in cardiac retransplant candidates and highlights the issue of sensitization portending greater risk for poor outcomes after TAH as bridge to retransplantation. *ASAIO Journal* XXX; XX:00–00.

Key Words: total artificial heart, cardiac retransplantation, sensitization

Over the past several decades, heart transplantation has emerged as an established treatment for end-stage heart failure, though survival is limited by primary graft failure and rejection of early post-transplantation and cardiac allograft vasculopathy later post-transplantation.[1] In selected patients with graft failure, cardiac retransplantation is an option, comprising 2.8% of adult heart transplants in the International Society for Heart and Lung Transplantation Registry.[1]

Patients undergoing cardiac retransplantation have comparable survival to those undergoing initial transplantation if retransplantation occurs >1 year after initial transplantation and is not performed for acute rejection.[2] Mechanical circulatory support (MCS) is not commonly performed as a bridge to cardiac retransplantation, though the total artificial heart (TAH) is a theoretically attractive option as it would remove the source of ongoing rejection and sensitization and provide biventricular support in the setting of restrictive physiology and/or biventricular allograft failure.[3] The purpose of this study was to review the Cedars-Sinai experience with the TAH as a bridge to cardiac retransplantation.

Cases

Three patients received TAH as a bridge to cardiac retransplantation at our institution between January 2012 and June 2017 (**Table 1** and **Figure 1**). In all cases, the initial orthotopic heart transplantation was performed using the bicaval surgical technique. Patient 1 had non-ischemic dilated cardiomyopathy. Her post-transplant course was significant for antibody-mediated rejection immediately post-transplant with donor-specific antibodies. She developed acute rejection 9 months post-transplant and cardiogenic shock requiring intra-aortic balloon pump 11 months post-transplant. Total artificial heart was placed 1 month later, 1-year post-transplant, and she was listed for retransplant 3 months later.

Patient 2 had congenital cardiomyopathy requiring transplantation as his fourth cardiac surgery. Five years later, he had antibody-mediated rejection. Six years post-transplant, he developed Grade 3 cardiac allograft vasculopathy with restrictive physiology. He was listed for retransplantation 7 years post-transplant. He suffered a cardiac arrest 2 days after being listed for retransplantation and was placed on venoarterial extracorporeal membrane oxygenation (VA-ECMO) support. He underwent TAH 8 days later.

Patient 3 had valvular cardiomyopathy requiring transplant. Seven years post-transplant he developed grade 3 cardiac allograft vasculopathy with restrictive physiology and underwent retransplant evaluation. He suffered a cardiac arrest requiring VA-ECMO 3 months after listing and had TAH placed 4 days later.

After TAH, length of stay in the intensive care unit was 51 days for patient 1, 11 days for patient 2, and 40 days for patient 3. Total hospital course was 59, 88, and 86 days for patients 1, 2, and 3, respectively. All patients received antiplatelet therapy with aspirin and anticoagulation with unfractionated heparin (monitored by the partial thromboplastin time assay) during hospitalization and warfarin after discharge with the exception of patient 3, who did not receive antiplatelet therapy due to recurrent lower gastrointestinal bleeding. Warfarin dosing was monitored using international normalized ratio (INR) testing, with goal INR 2.5–3.0 in patients 1 and 2 and goal 2.0–2.5 in patient 3 due to recurrent lower gastrointestinal bleeding.

Results

Patients 1 and 2 were highly sensitized at the time of TAH (**Table 1**) with calculated panel reactive antibodies (CPRA) for strong-binding antibodies of 93% and 64%, respectively. Patient 1 received post-TAH desensitization therapy with intravenous immunoglobulin with no effect on the CPRA. Her desensitization treatment was limited due to development of Pseudomonas bacteremia with presumed TAH involvement.

Patient 2 received desensitization therapy post-TAH with plasmapheresis, bortezomib, carfilzomib, and rituximab with no change in CPRA. Patient 3 was not sensitized and did not require desensitization therapy.

All patients suffered complications post-TAH (**Figure 1**). Patient 1 had TAH infection with Pseudomonas. Patient 2 had *Escherichia coli* pneumonia, *Enterobacter bacteremia*, and recurrent hemorrhagic strokes. Patient 3 had polymicrobial

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Table 1. Clinical characteristics.

	Patient 1	Patient 2	Patient 3
Clinical characteristics at the time of TAH implantation			
Age at TAH	39	25	63
Male sex	No	Yes	Yes
Body mass index	23	27	28
Etiology of cardiomyopathy	Non-ischemic	Congenital	Valvular
Prior sternotomies	1	3	1
Crossmatch*	Negative	Negative	Negative
Etiology of graft failure			
Cardiac allograft vasculopathy	No	Yes	Yes
Acute rejection	No	No	No
Pre-TAH dialysis	No	Yes	No
LVEF at time of TAH (%)	45	52	49
INTERMACS profile at TAH implant	3	1	1
Sensitization at HTx	Yes	No	No
HTx desensitization regimen	Bortezomib, Rituximab, IVIG	No	No
CPRA at time of TAH	93	64	0
Temporary MCS as bridge to TAH	IABP	VA-ECMO	VA-ECMO
Outcomes post-TAH			
Total LOS post-TAH (days)	59	88	86
LOS in ICU (days)	51	11	40
Transition to freedom driver (days)	44	81	50
Duration on freedom driver (days)	542	421	101
Total duration on TAH (days)	1315	502	151
Days to rehospitalization	237	33	6
Antiplatelet therapy on TAH	Aspirin 81 mg	Aspirin 325 mg twice daily	None
Anticoagulation therapy on TAH	Warfarin	Warfarin	Warfarin
Complications			
Systemic infection	Yes	Yes	Yes
Driveline infection	Yes	Yes	No
Thromboembolic event	Yes	No	No
CVA	No	Yes	Yes
Hemorrhagic event	Yes	Yes	Yes
GI bleed	Yes	Yes	Yes
Renal failure requiring dialysis	No	Yes	Yes
CPRA post-TAH	97	78	0
Desensitization strategy post-TAH	IVIG	Plasmapheresis, Bortezomib, Carfilzomib	None
Survival to cardiac retransplantation	No	No	Yes
Dual organ transplantation	No	No	Yes (HTx + DDKT)
Cause of death	Hemorrhage immediately post-retransplantation	Intracranial Hemorrhage	N/A

*Retrospective crossmatches were performed at the time of initial transplantation for all 3 patients and were negative by cell-dependent cytotoxicity and flow cytometry. As patient 1 was highly sensitized, she also had a prospective crossmatch that was negative for both cell-dependent cytotoxicity and flow cytometry.

CPRA, calculated panel reactive antibodies; CVA, cerebrovascular accident; DDKT, deceased donor kidney transplant; GI, gastrointestinal; HTx, heart transplantation; IABP, intraaortic balloon pump; IVIG, intravenous immunoglobulin; LOS, length of stay; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; TAH, total artificial heart; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

bacterial pneumonia, cytomegalovirus viremia, and recurrent lower gastrointestinal bleeding.

Patient 1 underwent redo heart transplantation *via* the bicaval technique but died shortly thereafter due to extensive bleeding and refractory shock attributed to TAH infection. Patient 2 died when care was withdrawn after a devastating hemorrhagic stroke. Patient 3 underwent heart transplantation *via* the bicaval technique and kidney transplantation 151 days post-TAH. His post-transplant course was complicated by recurrent gastrointestinal bleeding and respiratory failure. He was ultimately discharged home 139 days after retransplantation.

The operative reports and surgical pathology for the 2 patients who underwent cardiac retransplantation were reviewed; the presence of gross necrosis or fibrosis of the atrium cuff remnants was not described in either case.

Discussion

Nationally, experience with the TAH as bridge to cardiac retransplantation is limited.[4] In the UNOS registry between 2006 and 2016, only 13 patients received a TAH as bridge to retransplant, and the UNOS registry does not include patients with MCS who did not survive to retransplantation.[3] In a single-center analysis from January 2000 to February 2014 at Columbia University Medical Center, 11 patients underwent MCS as bridge to retransplantation, though the number of patients with TAH was not specified.[5]

The TAH is a theoretically feasible option in both acute rejection as it allows removal of the nidus promoting rejection, and in cardiac allograft vasculopathy where the biventricular involvement and restrictive physiology render left ventricular support alone less effective. Given the potential benefit and limited published experience of TAH as bridge to cardiac

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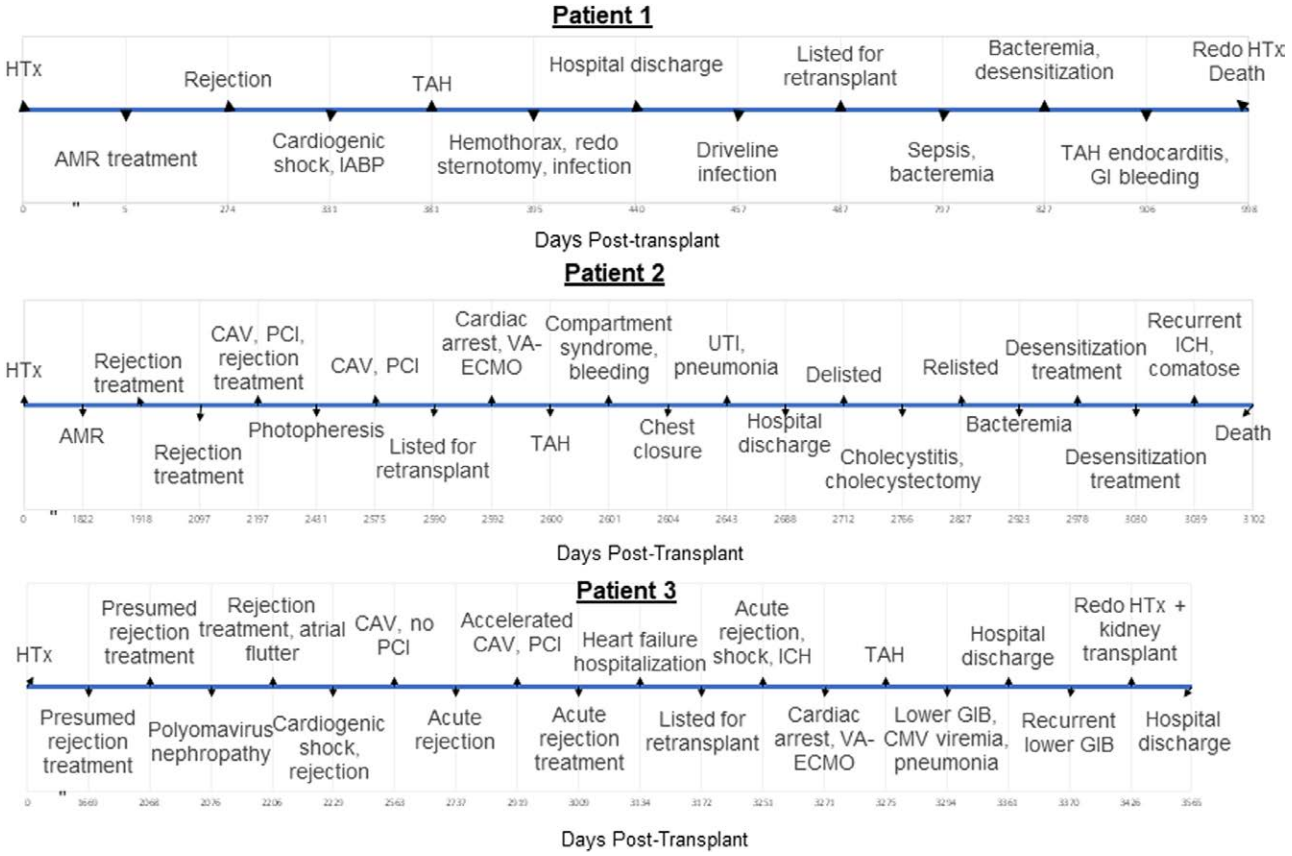

Figure 1. Post-transplant complications and clinical course. HTx, heart transplant; AMR, antibody-mediated rejection; IABP, intra-aortic balloon pump; TAH, total artificial heart; GI, gastrointestinal; CAV, cardiac allograft vasculopathy; PCI, percutaneous coronary intervention; VA-ECMO, venoarterial extracorporeal membrane oxygenation; UTI, urinary tract infection; ICH, intracranial hemorrhage; CMV, cytomegalovirus.

retransplantation, careful review of institutional experience is essential to determine the possible benefit of this strategy.

Our experience indicates that the use of TAH as a bridge to retransplant is a high-risk venture fraught with substantial morbidity and mortality. Two of the 3 patients required VA-ECMO before TAH, a scenario with high mortality even in primary heart transplant recipients. Only one of the 3 patients survived post-retransplantation, and this patient was the only patient who was not highly sensitized. Sensitization incurred high morbidity, as desensitization therapy likely resulted in the TAH infection responsible for the intraoperative death of patient 1 and refractory sensitization post-TAH rendered retransplantation an impossibility for patient 2. Patient 2 also suffered significant infectious complications as a result of desensitization therapy with a fatal hemorrhagic stroke in the setting of bacteremia, consistent with the observation that infection is a strong risk factor for hemorrhagic stroke.[6–8]

Conclusions

Based on this experience, we consider recurrent rejection with sensitization very high risk for TAH as bridge to retransplantation. Whether the new heart allocation system prioritizing patients with TAH as status 2 will allow for shorter wait times and less potential for waitlist complications remains uncertain. For patients with graft failure due to allograft vasculopathy who are not sensitized, TAH may be considered in selected patients in a shared decision-making discussion, understanding the significant morbidity involved.

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