Case Reports

The Man with 2 Hearts:

25 Years from Heterotopic to Orthotopic Heart Transplantation

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Substantial technological advances in mechanical circulatory support have caused a shift in the management of end-stage heart failure. From the 1970s through the 1990s, heterotopic heart transplantation was routinely performed in patients in whom orthotopic transplantation was likely to fail. Heterotopic heart transplantation is now performed less often because modern mechanical circulatory assist devices are routinely used as bridges to orthotopic transplantation; regardless, the operation has helped numerous patients who would not otherwise have received adequate allografts.

We describe the case of a man with idiopathic nonischemic cardiomyopathy who, at age 17, was given an ABO- and size-matched heterotopic allograft that was a complete human leukocyte antigen mismatch. The graft functioned normally for 20 years until the patient had a myocardial infarction that necessitated placement of a coronary artery stent. Subsequent treatments involved many interventions, including insertion of an intra-aortic balloon pump, medical therapy for heart failure, implantation of a total artificial heart, and, ultimately, orthotopic transplantation.

To our knowledge, our patient is the longest surviving recipient of a heterotopic heart transplant, with a remarkable 25-year graft survival despite poor histocompatibility and an almost complete lack of native heart function. The strategies used for his treatment make him a living case study that can add valuable information to the history of cardiac support.
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Heterotopic heart transplantation (HHTx) has been a treatment for end-stage heart failure since the 1970s. Typical indications have included a high transpulmonary pressure gradient (TPG) (>15 mmHg), donor–recipient size mismatches, and a high risk of graft rejection. In case of heterotopic allograft rejection, the native heart had the potential to provide some circulatory support.[1-3] When new circulatory support devices and medical therapies for pulmonary hypertension were introduced, the use of HHTx declined. Although HHTx has, on average, higher morbidity and mortality rates than does orthotopic transplantation, investigators[3] have suggested that the increased risks associated with receiving heterotopic cardiac allografts can be attributed to the indications for HHTx, such as size mismatch and high TPG, rather than to the procedure itself. As the use of ventricular assist devices increases and HHTx is performed less often, some clinicians[4] have questioned whether the need for immunosuppression outweighs the risks associated with a perpetually indwelling foreign body.

Previously, HHTx was used to prolong the lives of many patients who otherwise would not have received adequate allografts.[1] In a few case reports, patients have survived for up to 20 years after transplantation, with the most marked successes reported in pediatric patients whose donor hearts grew along with them.[5-9] We describe the case of perhaps the longest-surviving recipient of an adult heterotopic heart transplant. When the heart's function declined, a series of interventions culminated in successful orthotopic heart transplantation 25 years after the HHTx.

Case Report

In spring 1992, a 17-year-old boy presented at our institution with an exacerbation of idiopathic nonischemic dilated cardiomyopathy and pulmonary insufficiency. He was listed at status 1 on the heart transplant waiting list (panel-reactive antibody, 13%). He needed intensive care and inotropic agents before transplantation. A heart became available from an identically sized donor who was close in age and ABO-compatible (type AB); however, results of human leukocyte antigen (HLA) tests revealed a com-

plete mismatch, with no HLA-A, -B, or -DR antigens in common. At the time, the patient's relatively high immunologic risk for graft rejection related to his young age and degree of antigen mismatch was used to justify HHTx over orthotopic transplantation. In April 1992, HHTx was performed as previously described,[10] with biatrial anastomoses to the native atria (Fig. 1).

The patient's native heart function did not recover; the left ventricular ejection fraction (LVEF) was consistently below 0.15, with LV and right ventricular dilation and global hypokinesis. However, his donor heart function was excellent, with normal LV filling and an LVEF of 0.60. Atrial fibrillation and premature ventricular complexes early after HHTx were successfully managed after implantation of a pacemaker. Excellent graft function for 2 decades enabled the patient to live a moderately active life that included working full-time and playing sports with his children.

When the patient was 39 years old, 22 years after the initial transplantation (Fig. 2), he had hypertension, and coronary artery disease was found in the donor graft. In March 2013 at a different hospital, a left anterior descending coronary artery stent was placed after the patient had a non-ST-segment-elevation myocardial infarction (NSTEMI). After a period of hyperkinesis and improved LVEF, apical akinesis in the donor heart and an overall decline in cardiac function were observed. Figure 3 shows the patient's LVEF over 9 years, illustrating its rapid decline after the NSTEMI, along with a spike in pulmonary artery pressure; Figure 4 shows a modest increase in cardiac dimensions and an inconsistent-but-rising right atrial pressure. Table I documents the patient's declining heart function over time; his cardiac dimensions, LVEF, and pulmonary artery systolic pressure had been stable during the 7 years before the NSTEMI.

Five months after the NSTEMI, the patient was admitted to our hospital with decompensated heart failure and a decreased graft LVEF of 0.40. He was relisted at status 1A on the heart transplant waiting list; however, the procedure was contraindicated because of positive tissue crossmatches. His status was downgraded to 1B

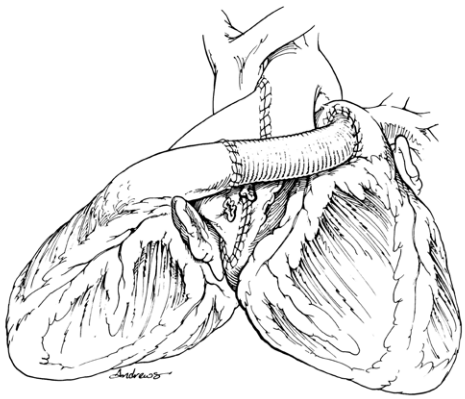

Fig. 1 *Illustration of biatrial heterotopic heart transplant configuration shows the donor heart aorta anastomosed to the patient's aorta, and the donor pulmonary artery anastomosed to the recipient pulmonary artery with use of an interposed Dacron tube-graft.*

Reprinted from Frazier OH, Okereke J, Cooley DA, Radovancevic B, Chandler LB, Powers P. Heterotopic heart transplantation in three patients at the Texas Heart Institute. Tex Heart Inst J *1985;12(3):221-32.*[10]

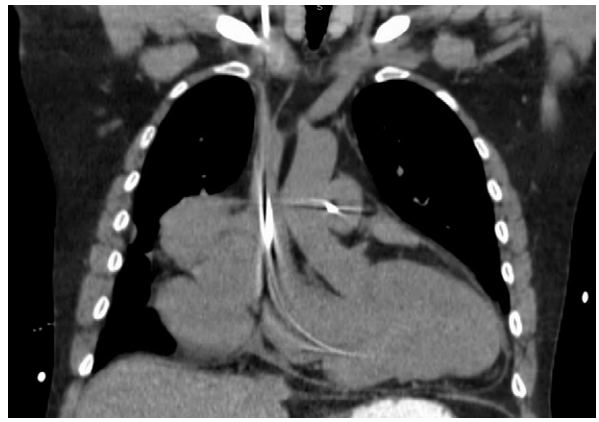

Fig. 2 *Computed tomogram (coronal view) 22 years after heterotopic heart transplantation shows the hearts in biatrial configuration, with pacemaker wires and Swan-Ganz catheter.*

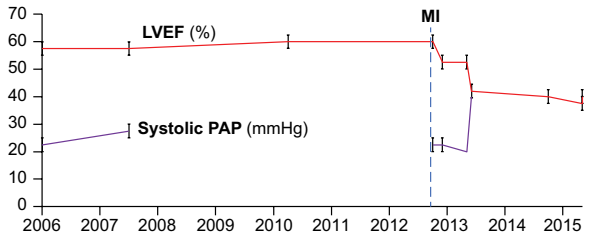

Fig. 3 *Graph shows decreasing left ventricular ejection fraction (LVEF) and increasing systolic pulmonary artery pressure (PAP) after the patient's myocardial infarction (MI) (dashed line).*

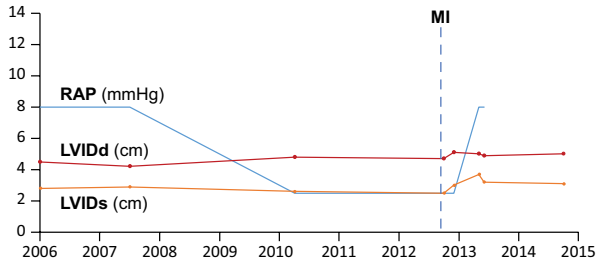

Fig. 4 *Graph shows a marked increase in the patient's right atrial pressure (RAP) and a slight increase in cardiac dimensions after the patient's myocardial infarction (MI).*

LVIDd = left ventricular internal diameter at end-diastole; LVIDs = left ventricular internal diameter at end-systole

in October 2013. His congestive heart failure was managed medically for 3 years. In May 2016, he was relisted at status 1A at a different facility.

An intra-aortic balloon pump (IABP) was placed in June 2016 while the patient was being considered for desensitization therapy for high panel-reactive antibody (>60%). Rapid decompensation during a cardiac catheterization procedure that same month prompted arteriovenous extracorporeal membrane oxygenation. Because of an immunologic obstacle to transplantation, the patient's native heart was replaced with a total artificial heart (TAH) as a bridge to transplantation; the circulation to the heterotopic donor heart was excluded as much as possible. The patient's postoperative course was complicated by multiple episodes of bacteremia and circuit thrombosis, the latter probably caused in part by incomplete exclusion of the heterotopic graft from the circulation. However, TAH support enabled desensitization therapy with therapeutic plasma exchange.

After approximately 6 months of TAH support and frequent plasma exchanges, the patient underwent orthotopic heart transplantation in January 2017 to replace the TAH. The heterotopic graft was removed at that time. As of January 2018, the patient was alive, 25 years after the initial HHTx.

Discussion

Graft and patient survival rates after orthotopic transplantation are higher than those after HHTx; nevertheless, HHTx can be a life-saving and durable procedure. Data have also supported the concept of a heterotopic graft as a biological heart-assist device.[11] Although reliable mechanical ventricular assist devices have become commonplace, the only support devices available when our patient underwent initial transplantation were pulsatile. In addition, the IABP and TAH, as used in his treatment, are mechanical options that can provide conceptually similar bridge-to-transplantation support, although both are associated with considerable morbidity rates during the waiting period.[12-14] The TAH, which was used in a heroic and still-experimental fashion in his case, can provide total circulatory support; however, its placement can be complicated in the presence of aberrant anatomy such as a dominant heterotopic cardiac graft.

Poor histocompatibility in a donor organ, as in this patient, has been strongly correlated with reduced graft survival over time, albeit less so for hearts than for other solid-organ transplants, such as kidneys.[15] This effect has been tied most closely to mismatches at the HLA-DR locus.[16] The effects of HLA-A and -B mismatches seemingly manifest themselves primarily in the short term (within 1 yr of transplantation), whereas DR mismatch is thought to contribute most to the number and severity of rejection episodes in the long term, in addition to higher in-hospital mortality rates.[17,18]

An HLA mismatch has also been implicated in graft vasculopathy. Despite the limitations of the studies designed to clarify the relationship between poor histocompatibility and vasculopathy, multiple rejection episodes, particularly beyond the first year after transplantation,

TABLE I. The Patient's Cardiac Events and Decline in Condition

Time	LVEF	Systolic PAP (mmHg)	RAP (mmHg)	LVIDd (cm)	LVIDs (cm)
2006 June	0.55–0.60	20–25	6–10	4.5	2.8
2007 December	0.55–0.60	25–30	6–10	4.2	2.9
2010 September	0.60	—	0–5	4.8	2.6
2013 March[a]	>0.60	20–25	0–5	4.7	2.5
May[b]	0.50–0.55	20–25	0–5	5.1	3
October[c]	0.50–0.55	20	6–10	5	3.7
November	0.40–0.44	40	6–10	4.9	3.2
2015 March	0.40	—	—	5	3.1
October	0.35–0.39	—	11–15	—	—
October	0.40	—	6–10	5.2	4.3
2016 March	0.45–0.49	25–30	6–10	4.4	2.2

LVEF = left ventricular ejection fraction; LVIDd = left ventricular internal diameter at end-diastole; LVIDs = left ventricular internal diameter at end-systole; PAP = pulmonary artery pressure; RAP = right atrial pressure

[a] Left anterior descending coronary artery stent placed after non-ST-segment-elevation myocardial infarction.

[b] Patient admitted in August 2013 for decompensated congestive heart failure (status 1A on transplant waiting list).

[c] Patient discharged from hospital (status 1B on transplant waiting list).

have been correlated with cardiac allograft vasculopathy.[19,20] In turn, graft vasculopathy has been described as a type of chronic rejection. Similar to overall trends in rejection, graft vasculopathy seems to be more frequent in patients with complete HLA-DR mismatch.[20]

Our patient survived for 25 years with a heterotopic cardiac allograft, despite poor histocompatibility in the donor organ and almost no native heart function. Chronic rejection probably contributed to the graft vasculopathy that led to his NSTEMI and the ultimate loss of graft function. A 25-year graft survival after HHTx has been reported in only one other case, that of an elderly man in France; however, his survival beyond that time is unknown.[8]

Of note, despite various challenges, HHTx maintains one advantage over all other current cardiac support therapies: heterotopic heart recipients do not depend on a power supply. Whereas all bridge-to-transplantation options may involve pharmaceutical therapy, HHTx enables improved mobility and freedom; our patient had an active life during his 25 years with a heterotopic graft.

Our patient's treatment course involved most of the interventions available in the field of cardiac support. He underwent successful HHTx, coronary stenting of the donor heart, IABP support and medical therapy for heart failure, TAH implantation, and ultimately orthotopic transplantation. His desire to continue treatment has enabled us to advance the art and science of managing the failing heart.

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