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Heterotopic Heart Transplantation: The United States Experience

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ABSTRACT

Introduction: More than 3 decades have passed since the first heterotopic heart transplantation (HHT) was reported. Nowadays, this surgical technique is used rarely, and only in patients who do not qualify for standard orthotopic heart transplantation (OHT). Current indications mainly comprise refractory pulmonary hypertension and a donor–recipient size mismatch (>20%). The objective of this study was to analyze the United States experience with HHT.

Patients and Methods: The United Network for Organ Sharing (UNOS) database between 1987 and 2007 was analyzed. Patients who underwent heart transplantation were enrolled in this study. Patients with missing transplant dates or history of retransplantation were excluded.

Results: A total of 41,379 patients underwent OHT and 178 HHT; 32,361 and 111 patients, respectively, were enrolled. Overall 1-, 5-, and 10-year survival was significantly ($P < .001$) better in OHT (87.7%, 74.4%, 54.4%) than HHT patients (83.8%, 59%, 35.1%). Survival in patients with transpulmonary gradients (TPG) >15 mmHg was 86.6 %, 73.3%, and 57.4% in the OHT and 93.8%, 64.8%, and 48.6% in the HHT group ($P = .35$). Pretransplant criteria (HHT versus OHT) with statistically significant differences ($P < .05$) were as follows (mean + SD): recipient weight, 78.9 + 19.9 versus 74.1 + 23.4 kg; recipient height, 174.9 + 13.9 versus 168 + 25.1 cm; and TPG 12.1 + 7.2 versus 9.6 + 6.3 mmHg.

Conclusions: The results show that HHT remains a feasible option in a highly selected patient population, with overall good results.

INTRODUCTION

More than 3 decades have passed since Barnard and Losman reported the first human heterotopic heart transplantation (HHT) in 1974, 7 years after reporting the first orthotopic heart transplantation (OHT) [Barnard 1967; Barnard 1975]. In HHT, the recipient diseased heart is preserved and the donor heart is implanted parallel to the existing heart. Despite certain advantages of this technique over the conventional orthotopic approach, HHT is nowadays rarely utilized. This surgical technique, however, evolved out of the limitations of OHT in the precyclosporine era, namely rejection-related donor heart malfunction in the immediate postoperative period and right ventricular failure in patients with preexisting pulmonary hypertension. The "piggy-backed" heart allowed the native heart to provide auxiliary circulatory support during episodes of severe allograft rejection [Novitzky1984] and would serve as a "biological heart assist device" in patients with moderate-to-severe pulmonary hypertension [Barnard 1975]. Two techniques of HHT have been previously described. The original technique is performed as a left heart assist only, and the later modified technique provides biventricular assistance [Barnard 1975; Barnard1977; Barnard1979].

With the introduction of more effective immunosuppressive agents (e.g. cyclosporine), however, and subsequent better rejection management, OHT has been increasingly used, with overall superior results [Desruennes1989; Kawaguchi1989; Ridley1992]. Thus, OHT has now become the configuration of choice and is exclusively utilized at most centers worldwide.

Nonetheless, a few centers still perform HHT in patients who do not qualify for the standard orthotopic procedure. Specific indications mainly include: (a) refractory recipient pulmonary hypertension in which the untrained donor right ventricle will not be able to overcome the pressure in the pulmonary vasculature, with subsequent right heart failure; (b) a significant donor–recipient size mismatch (≥20%), with the smaller donor being used for larger recipients [Reichenspurner1989]; and in some cases even (c) the utilization of suboptimal or marginal donor organs (e.g. long ischemic times, prolonged donor cardiopulmonary resuscitation) [Konertz 1988; Livi 1990; Newcomb 2004; Chiu 2006].

The aim of this study was to analyze the United States experience with HHT between 1987 and 2007, and to compare the results with OHT during the same time period.

METHODS

This study was conducted with approval from the Institutional Review Board of the Baylor College of Medicine, Houston, TX. Patients who have undergone heart transplantation were enrolled through the United Network for Organ Sharing (UNOS) Organ Procurement and Transplantation Network (OPTN) database. This database contains patient

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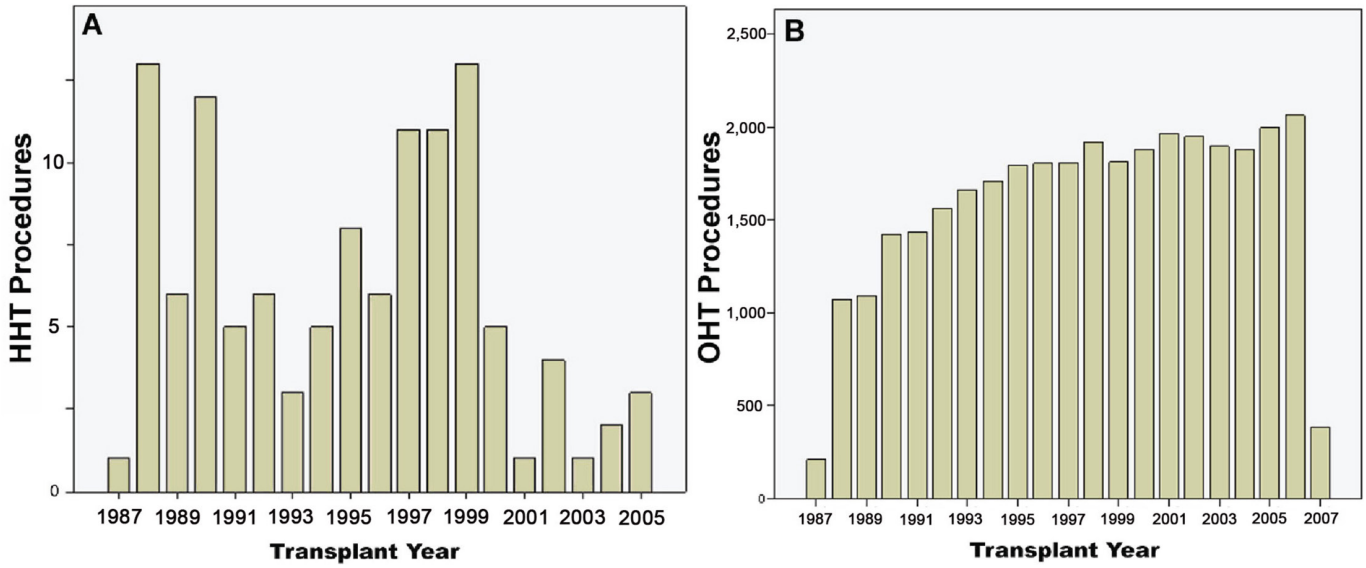

Figure 1. Overall number of transplants between October 1, 1987, and May 1, 2007. A). HHT (n = 178). B). OHT (n = 41,379).

and graft outcomes for more than 58,000 patients who have undergone thoracic organ transplantation in the United States between October 1, 1987, and May 1, 2007. Exclusion criteria used for this study were history of retransplantation and missing transplant dates.

Descriptive statistics were calculated using all available pretransplant and perioperative variables. These data were compared using a chi-square test for categorical variables and Student t-test for continuous variables.

Patient survival was assessed using the Kaplan-Meier method, and survival rates of HHT and OHT patients, as well as, subgroups (HHT with ischemic cardiomyopathy [ICM] or dilated cardiomyopathy [DCM] versus OHT with ICM or DCM, HHT with transpulmonary gradients [TPG] >15 versus OHT with TPG >15 mmHg) were compared with the log-rank test.

A Cox proportional hazards model was utilized to verify variable association with survival in a multivariate analysis for the entire heart transplant cohort (OHT and HHT), and separately for the HHT and OHT groups. Only variables with <20% missing data were studied; in particular, these variables included recipient and donor age, ethnicity, sex, pretransplant diagnosis, ischemic time, and treatment type. All statistical analysis was performed with SPSS (SPSS Corporation, Chicago, IL, USA). Descriptive statistics are presented as mean values with standard deviation (SD) or numbers with percentage of overall frequencies. A P value of <.05 was used to determine statistical significance.

RESULTS

Heart Transplant Frequencies

Between October 1, 1987, and May 1, 2007, 41,557 heart transplant procedures were reported to UNOS. Of these procedures, 41,379 (99.6%) were performed in the orthotopic and 178 (0.4%) in the heterotopic configuration (Figure 1). A total of 32,361 patients with OHT and 111 patients with HHT met the inclusion criteria and were enrolled in this study.

Age Distribution among Groups

There was no statistically significant difference in age distribution among the transplant recipients in the HHT group and recipients in the OHT group (P = .14), with a mean + SD age of 49.5 + 13.5 years and 47.6 + 17.0 years, respectively (Table 1). In the HHT group, the frequency of transplant procedures peaked at 53 years. Frequencies of transplant procedures in the OHT group followed a bimodal distribution, with the first peak in the first year of life and a second peak at 52 years (Figure 2).

Patient Demographics

Recipient and donor characteristics were assessed, and the differences between the 2 groups (HHT versus OHT) were tested for statistical significance (Table 1).

Characteristics without significant differences included recipient sex, with 82.9% male and 17.1% female in the HHT group and 76.6% male and 23.4% female in the OHT group (P = .12); donor sex, with 61.3% male and 38.7% female in the HHT group versus 69.6% and 30.4% in the OHT group (P = .058); ethnicity, with 73% white, 16.2% black, and 10.8% Hispanic in the HHT group and 79.3% white, 12.5% black, 5.8% Hispanic, 1.6% Asian, and 1% others In the OHT group (P = .23). The pretransplant diagnosis was similar in both groups, with 44.1% DCM, 46.8% ICM, 3.6% restrictive cardiomyopathy, 2.7% valvular heart disease, 0.9% congenital heart disease, and 1.8% other in the HHT group versus 41.5% dilated cardiomyopathy, 45.6% ischemic cardiomyopathy, 1.6% restrictive cardiomyopathy, 1.3% hypertrophic cardiomyopathy, 2.7% valvular heart disease, 5.9% congenital heart disease, and 1.4% other in the OHT group (P = .32). Donor age ranged from 1 to 58 years (mean of

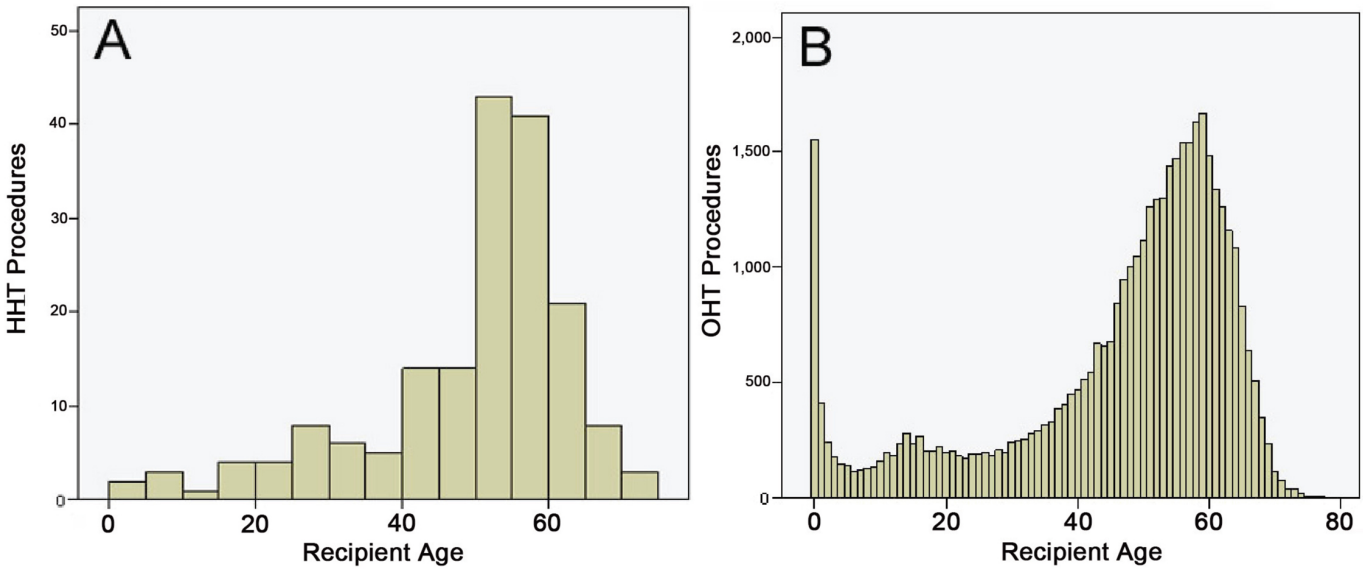

Figure 2. Age distribution among groups. A). HHT, median age 53 years. B). OHT, median age 52 years.

26.8 + 11.9 years) in the HHT group versus 0 to 73 years (mean of 28.4 + 13.6 years) in the OHT group (P = .17). Donor weight (P = .22) and donor height (P = .57) were 70.5 + 18.8 kg and 165.3 + 24.3 cm, respectively, in the HHT group and 72.9 + 23.2 kg and 167 + 27.6 cm in the OHT group; recipient body mass index was 25.6 + 6.1 kg/m^2 in the HHT group and 26.9 + 7 kg/m^2 in the OHT group (P = .96); recipient creatinine was 1.5 + 0.7 mg/dL in the HHT and 1.3 + 1.3 mg/dL in the OHT group (P = .23); cardiac output was 4.3 + 1.4 L/min in the HHT group and 4.1 + 1.4 in the OHT group (P = .57); ischemic time was 3.2 + 1.3 h in the HHT group and 2.9 + 1.1 h in the OHT group (P = .18); and post-transplant hospital stay averaged at 18.6 + 22.8 days in the HHT and 20 + 42.1 days in the OHT group (P = .74).

Characteristics that reached statistical significance included recipient weight and height, donor/recipient weight and height ratio, transpulmonary gradient, and waiting list time. Recipient weight was significantly (P = .03) higher in the HHT patients than in the OHT patients (78.9 + 19.9 kg and 74.1 + 23.4 kg, respectively). Recipient height was significantly (P < .001) higher in the HHT than in the OHT group (174.9 + 13.9 cm and 168 + 25.1 cm, respectively). The notion that smaller donor organs were used in larger recipients is supported by the results of donor/recipient weight and height ratios, which were significantly different between the 2 groups. The donor/recipient weight ratio was 0.93 + 0.25 in the HHT and 1.1 + 0.44 in the OHT group (P = .01). The donor/recipient height ratio was 0.95 + 0.13 in the HHT and 1.0 + 0.18 in the OHT group (P = .003). Also, in support of the notion that patients who underwent HHT had clinically significant pulmonary hypertension is the finding of a significantly higher transpulmonary gradient in the HHT versus the OHT group. Accordingly, the transpulmonary gradient was 12.1 + 7.2 in the HHT and 9.6 + 6.3 in the OHT group (P = .005).

Waiting list time was also significantly (P = .02) longer in the HHT group versus the OHT group (254.4 + 342.3 days versus 190.3 + 303.4 days respectively).

Cause of Death

Cause of death has been reported in 12,144 heart transplant recipients. Seventy-five were reported in the HHT group and 12,069 in the OHT group (Table 2). Graft failure, as a cause of death due to primary failure or acute and chronic rejection, was significantly (P = .011) more frequent in the HHT than in the OHT cohort (Table 2). Other causes of death, such as infections; cardiovascular, pulmonary, or cerebrovascular hemorrhage; malignancies; renal failure; or multiorgan failure did not show a significant difference between the 2 groups.

Kaplan-Meier Survival Analysis

HHT versus OHT: Patient survival was analyzed using the Kaplan-Meier method and the differences in survival were tested for significance using the log-rank test. The Kaplan-Meier curve demonstrating the overall posttransplant patient survival is shown in Figure 3. Overall, 1-, 5-, and 10-year survival was significantly (P < .001) better in the OHT group (87.7%, 74.4%, 54,4%) than in the HHT group (83.8%, 59%, 35.1%).

Ischemic versus Nonischemic Cardiomyopathy: Survival in patients with nonischemic cardiomyopathy (DCM) who underwent OHT (89.5%, 75.7%, 57.9%) was significantly (P < .001) better than in patients with ICM (86.1%, 72%, 48.5%). Although survival in patients with DCM who underwent HHT (87.7%, 62.7%, 36.5%) was better than in patients. with ICM who underwent HHT (78.8%, 52.1%, 32.7%), this difference did not reach statistical significance (P = .19) (Figure 4).

HHT versus OHT in patients with TPG >15: Another subgroup analysis, assessing survival in patients with a TPG

Table 1. Recipient and Donor Characteristics for HHT and OHT Patients

Description	HHT (n = 111), No. (%) or Mean ± SD	OHT (n = 32,361), No. (%) or Mean ± SD	*P* Value
Recipient sex			.12
Male	92 (82.9%)	24,778 (76.6%)	
Female	19 (17.1%)	7583 (23.4%)	
Donor sex			.058
Male	68 (61.3%)	22,512 (69.6%)	
Female	43 (38.7%)	9849 (30.4%	
Recipient ethnicity			.23
White	81 (73.0%)	25,664 (79.3%)	
Black	18 (16.2%)	4030 (12.5%)	
Hispanic	12 (10.8%)	1876 (5.8%)	
Asian	None	504 (1.6%)	
Other	None	287 (1%)	
Pretransplant diagnosis			.32
DCM	49 (44.1%)	13,443 (41.5%)	
ICM	52 (46.8%)	14,751 (45.6%)	
Restrictive cardiomyopathy	4 (3.6%)	521 (1.6%)	
Hypertrophic cardiomyopathy	None	426 (1.3%)	
Valvular heart disease	3 (2.7%)	864 (2.7%)	
Congenital heart disease	1 (0.9%)	1897 (5.9%)	
Other	2 (1.8%)	459 (1.4%)	
Recipient age, years	49.5 + 13.5	47.6 + 17.0	.14
Age range, years	1 - 70	0 - 78	
Donor age, years	26.8 + 11.9	28.4 + 13.6	.17
Age range, years	1 - 58	0 -73	
Recipient weight, kg	78.9 + 19.9	74.1 + 23.4	.03*
Recipient height, cm	174.9 + 13.9	168 + 25.1	< .001†
Donor weight, kg	70.5 + 18.8	72.9 + 23.2	.22
Donor height, cm	165.3 + 24.3	167.0 + 27.6	.57
Donor/Recipient weight ratio	0.93 + 0.25	1.1 + 0.44	.01*
Donor/Recipient height ratio	0.95 + 0.13	1.0 + 0.18	.003†
Recipient body mass index	25.6 + 6.1	26.9 + 7.0	.96
Recipient creatinine, mg/dL	1.5 + 0.7	1.3 + 1.3	.23
Recipient cardiac output, L/min	4.3 + 1.4	4.1 + 1.4	.57
TPG, mmHg	12.1 + 7.2	9.6 + 6.3	.005†
Ischemic time, hours	3.2 + 1.3	2.9 + 1.1	.18
Waiting list time, days	254.4 + 342.3	190.3 + 303.4	.026*
Posttransplant hospital days	18.6 + 22.8	20 + 42.1	.74

*Denotes differences that reach statistical significance of $P < .05$.
†Denotes differences that reach statistical significance of $P < .005$.

Table 2. Causes of Death for HHT and OHT

Description	HHT (n = 75), No. (%)	OHT (n = 12,069), No. (%)	*P* Value
Graft failure	19 (25.3)	1844 (15.3)	.011*
Primary	6 (8)	350 (2.9)	
Hyperacute rejection	None	67 (0.5)	
Acute rejection	2 (2.6)	701 (5.8)	
Chronic rejection	4 (5.3)	353 (2.9)	
Other	7 (9.3)	373 (3)	
Infection	7 (9.3)	1735 (14.4)	.396
Bacterial	4 (5.3)	984 (8.1)	
Viral	2 (2.6)	207 (1.7)	
Other	2 (2.6)	544 (4.5)	
Cardiovascular	19 (25.3)	2254 (18.6)	.108
Myocardial infarction	2 (2.6)	252 (2)	
Cardiac arrest	8 (10.6)	932 (7.7)	
Arterial embolism	1 (1.3)	13 (0.1)	
Ventricular failure	2 (2.6)	125 (1)	
Coronary artery disease	3 (3.9)	503 (4.1)	
Rhythm disorder	1 (1.3)	86 (0.7)	
Other	2 (2.6)	343 (2.8)	
Pulmonary	3 (4)	514 (4.3)	.945
Respiratory failure	1 (1.3)	262 (2.1)	
Pulmonary embolism	1 (1.3)	99 (0.8)	
Other	1 (1.3)	153 (1.3)	
Cerebrovascular	None	439 (3.6)	.096
Hemorrhage	None	194 (1.6)	.274
Malignancy	6 (8)	1484 (12.3)	.282
Renal failure	4 (5.3)	406 (3.4)	.321
Multiple organ failure	2 (2.7)	874 (7.2)	.135
Other	6 (8)	1130 (9.4)	.454

*Denotes differences that reach statistical significance of $P < .05$.

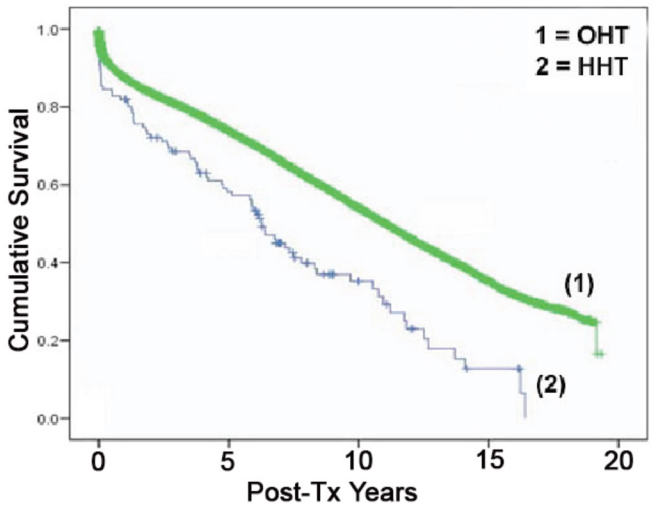

Figure 3. Kaplan-Meier survival analysis: OHT (1) versus HHT (2). Survival: 1-, 5-, 10-year (1) 87.7%, 74.4%, 54.4%; (2) 83.8%, 59%, 35.1% ($P < .001$).

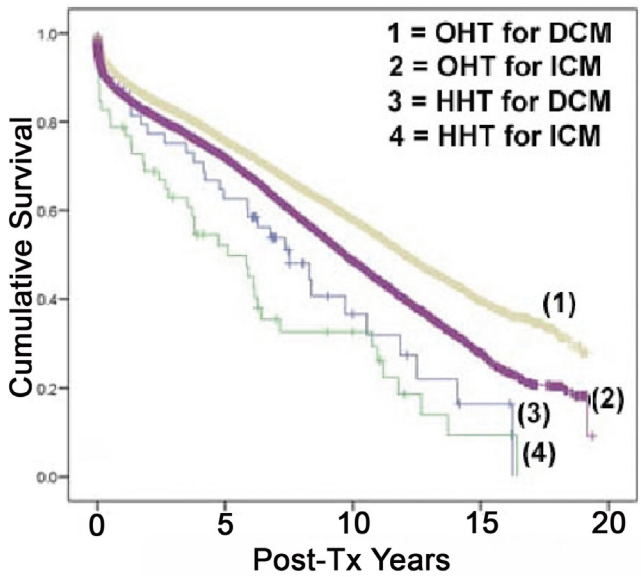

Figure 4. Kaplan-Meier survival analysis: OHT for DCM (1) and OHT for ICM (2) versus HHT for DCM (3) and HHT for ICM (4). Survival: 1-, 5-, 10-year (1) 89.5%, 75.7%, 57.9%; (2) 86.1%, 72%, 48.5% ($P < .001$); (3) 87.7%, 62.7%, 36.5%; (4) 78.8%, 52.1%, 32.7% ($P = .19$).

>15 mmHg, showed no significant differences between patients who underwent OHT (n = 3130 [TPG, 19.4 + 5.7 mmHg]) versus HHT (n = 16 [TPG, 20.5 + 6.7 mmHg]) ($P = .35$); 1-, 5-, and 10-year survival was 86.6 %, 73.3%, 57.4% in the OHT group and 93.8%, 64.8%, and 48.6% in the HHT group (Figure 5). Hence, the previously described survival benefit of OHT over HHT disappeared in this selected patient population with clinically significant pulmonary hypertension.

Predictors of Patient Survival

In order to verify variable associations with posttransplant survival, a Cox regression for survival analysis was performed for all patients who underwent heart transplantation, and separately for the 2 cohorts who underwent HHT or OHT (Table 3).

This multivariate analysis of the entire population (HHT and OHT) considered different pretransplant variables (recipient and donor age, ethnicity, sex, pretransplant diagnosis, ischemic time, and treatment [Tx] type) and demonstrated that recipient age (hazard ratio = 1.011, $P < .001$), donor age (hazard ratio = 1.011, $P < .001$), black ethnicity (hazard ratio = 1.465, $P < .001$), ischemic cardiomyopathy (hazard ratio =

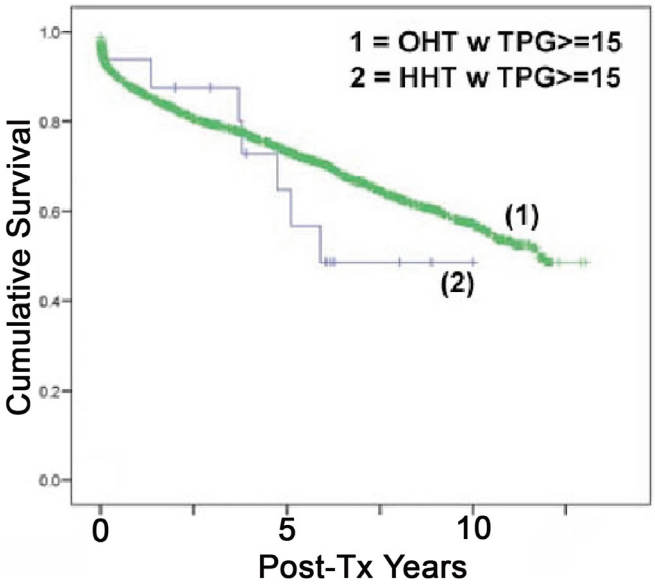

Figure 5. Kaplan-Meier survival analysis: OHT for TPG >15 mmHg (1) versus HHT for TPG >15 mmHg (2). Survival: 1-, 5-, 10-year, 86.6%, 73.3%, 57.4% (1); 93.8%, 64.8%, 48.6% (2) (P = .35).

1.214, P < .001), pretransplant cancer (hazard ratio = 3.312, P < .001), ischemic time (hazard ratio = 1.026, P = .005), and OHT (hazard ratio = 0.519, P < .001) were all independently correlated with posttransplant survival.

In the HHT population, only Hispanic ethnicity (hazard ratio = 0.268, P < .036) was independently correlated with posttransplant survival.

The results of the OHT cohort reflected the findings for the entire population (OHT and HHT). Recipient age (hazard ratio = 1.011, P < .001), donor age (hazard ratio = 1.011, P < .001), black ethnicity (hazard ratio = 1.465, P < .001), ischemic cardiomyopathy (hazard ratio = 1.215, P < .001), pretransplant cancer (hazard ratio = 3.314, P = .001), and ischemic time (hazard ratio = 1.026, P < .007) independently correlated with posttransplant survival (Table 3).

DISCUSSION

Heterotopic heart transplantation was first performed in 1974, with the main advantage that the native heart function could be preserved in cases of life-threatening acute rejection episodes [Barnard1977]. Moreover, in patients with persistent pulmonary hypertension, the use of the heart allograft in the heterotopic position prevented failure of the unconditioned right donor ventricle [Barnard1979]. Others have also proposed and described the emergency use of donor hearts in the heterotopic configuration when no hearts of suitable size for orthotopic transplantation could be identified [Cooper 1986; Konertz 1988].

Nonetheless, with the emergence of more potent immunosuppressants (cyclosporine A in 1984) and improving results with OHT, the technically more challenging heterotopic approach lost its major clinical significance. Heterotopic heart transplantation is nowadays used in only a few transplant centers and in a highly selected patient population [Newcomb 2004]. In this study we examined the outcomes of patients who underwent HHT in the United States between 1987 and 2007. With patients enrolled through the UNOS database, this study population includes the worldwide largest cohort of patients who have undergone this rare procedure.

The first objective for this study was to describe the patients and analyze survival of HHT compared to the conventional OHT approach. Of 41,557 heart transplants performed in the United States during the aforementioned period, only a very small fraction (0.4%) was done in the heterotopic configuration. The 2 populations had very similar demographics and physiologic characteristics, and could be discriminated only in regard to larger size and greater weight and smaller donor/recipient height and weight ratio, as well as higher TPG and significantly longer waiting list times (likely due to the more difficult allocation of a suitable donor organ) in the HHT population (Table 1). This finding supports the notion that heterotopic transplants were mainly performed for donor–recipient size mismatches (small donors for larger recipients) and in patients who are not suitable for OHT due to clinically significant pulmonary hypertension. The analysis demonstrates that the 1-, 5-, and 10-year actuarial survival after HHT was 83.3%, 59%, and 35.1%. Although survival was significantly better in the OHT group (87.7%, 74.4%, 54.4%), the results achieved with HHT have to be favorably regarded, considering that these patients were otherwise not candidates for transplantation due to their comorbidities and larger stature. A subgroup analysis showed that survival after transplantation for DCM was better than for ICM. This finding was consistent in both groups, although it reached statistical significance only in the OHT group (Figure 4). Not necessarily surprising was the observation that the survival benefit of OHT disappeared in the subgroup of patients with TPG of equal or greater than 15 mmHG. Moreover, with a 1-year survival rate of 93.8% in the HHT group, it even exceeded the survival achieved with OHT (86.6%) (Figure 5).

Our second aim was to identify factors that may help predict survival of patients who undergo HHT. Interestingly, the average ischemic time was longer in the HHT than in the OHT group (3.2 hours versus 2.9 hours). Although it did not reach statistical significance, the longer total ischemic time may possibly reflect the more difficult and complex surgical technique for HHT compared to the conventional OHT approach.

In an Australian study, Newcomb et al reported significantly longer ischemic times in their HHT patient population [Newcomb 2004]. This, however, was deliberately taken into account in order to address the shortage of donor organs and to increase the available donor pool. Thus, allografts were procured from all over the Australian continent and New Zealand, thereby causing the rather long ischemic times (average 6.1 hours). The authors did notice impaired allograft function in 4 out of overall 20 heterotopic cardiac allografts with ischemic times exceeding 7 hours. This clinical condition mandated high-dose inotropic support postoperatively and implementation of intra-aortic balloon counterpulsation,

Table 3. Proportional Hazards Regression (Cox Regression) for Survival: Analysis for All Patients (Overall) and HHT or OHT Recipients

Patients	Hazard Ratio	95% Confidence Interval	*P* Value
Overall (HHT and OHT)			
Recipient age (per year)	1.011	1.009–1.012	<.001†
Donor age (per year)	1.011	1.009–1.012	<.001†
Ethnicity			
Black	1.465	1.384–1.551	<.001†
Hispanic and others	0.965	0.889–1.047	.391
Female	0.979	0.934–1.026	.378
Diagnosis			
Ischemic cardiomyopathy	1.214	1.164–1.267	<.001†
Restrictive, hypertrophic, and valvular cardiomyopathy	1.044	0.956–1.140	.334
Congenital cardiomyopathy	0.941	0.831–1.066	.339
Cancer	3.312	1.654–6.632	.001†
Other	1.009	0.832–1.225	.924
Ischemic time (per minute)	1.026	1.008–1.045	.005*
OHT	0.519	0.406–0.663	<.001†
HHT			
Recipient age (per year)	1.014	0.988–1.041	.299
Donor age (per year)	1.012	0.989–1.035	.31
Ethnicity			
Black	1.51	0.683 - 3.336	.308
Hispanic	0.268	0.078–0.915	.036*
Female	1.001	0.375–2.674	.999
Diagnosis			
Ischemic cardiomyopathy	1.169	0.657–2.081	.595
Restrictive, hypertrophic, and valvular cardiomyopathy	1.897	0.412–8.726	.411
Ischemic time (per minute)	1.065	0.860–1.320	.563
OHT			
Recipient age (per year)	1.011	1.009–1.012	<.001†
Donor age (per year)	1.011	1.009–1.012	<.001†
Ethnicity			
Black	1.465	1.383–1.551	<.001†
Hispanic and others	0.974	0.897–1.057	.524
Female	0.98	0.935–1.028	.403
Diagnosis			
Ischemic cardiomyopathy	1.215	1.164–1.268	<.001†
Restrictive, hypertrophic, and valvular cardiomyopathy	1.043	0.955–1.139	.347
Congenital cardiomyopathy	0.941	0.831–1.066	.342
Cancer	3.314	1.655–6.636	.001†
Other	1.019	0.84–1.237	.847
Ischemic time (per minute)	1.026	1.007–1.045	.007*

*Denotes differences that reach statistical significance of $P < .05$.
†Denotes differences that reach statistical significance of $P \leq .005$.

as well as synchronization of donor and recipient heart pacing. Nevertheless, with this aggressive treatment, full function was restored in all cases after a maximum of 72 hours.

Our multivariate analysis identified ischemic time as a variable, which was adversely related to posttransplant outcomes in our entire patient cohort and in the orthotopic subgroup (Table 3). Ischemic time, however, could not be identified as a significant independent risk factor for posttransplant outcomes in the heterotopic transplant group alone. This may be related to the relatively smaller size of the heterotopic transplant group, or possibly mean that the impact of ischemic time on posttransplant survival may be less significant after HHT than it is after OHT. This latter explanation, however, remains speculative, especially since the heterotopic transplant recipients in this study (with less ischemic time) had an overall better actuarial survival than that reported by the Australian group (1- and 5-year survival of 84% versus 60% and 59 % versus 15%, respectively). Additional prospective studies are needed to clarify the impact of ischemic time on outcomes after HHT.

Other factors that were adversely related to outcomes after OHT were recipient and donor age, black ethnicity, ischemic cardiomyopathy, and pretransplant cancer. In the HHT group, Hispanic ethnicity was found to be a protective factor. The analysis of the overall population (HHT and OHT) showed that OHT was also found to be a protective factor (Table 3), which supports the findings of the Kaplan-Meier analysis that shows that survival after OHT is superior to survival after HHT (Figure 3).

Pulmonary hypertension remains a relative contraindication for OHT. In the past, different options were exploited to treat patients with end-stage heart failure who were not candidates for standard OHT. For instance, OHT using larger donors [Kawaguchi 1989] or with a preconditioned allograft derived from a domino heart-lung transplant procedure [Anyanwu 2002], or even combined heart and lung transplantation. The latter option, however, remains controversial in times of donor organ shortage and given the poorer outcomes with combined heart/lung transplantation [Chapelier 1993],

Nakatani et al. reported good intermediate-term survival in patients with raised pulmonary pressures and subsequent HHT compared to OHT recipients [Nakatani 1989]. The authors also described a normalization of pulmonary pressures over the course of 12 months. This group and others reported the feasibility of reversal of persistent secondary pulmonary hypertension with unloading of the native left ventricle by means of a "biological heart assist device" (the heterotopic allograft) [Villanueva 1989]. This was further supported by future observations that mechanical circulatory support devices (such as left ventricular assist devices [LVAD]) could also be used in patients with end-stage heart failure and secondary pulmonary hypertension, for the purpose of achieving normalization of pulmonary pressures while bridging the patient to OHT [Martin 2004; Salzberg 2005; Etz 2007; Zimpfer 2007]. This important clinical observation that similar effects can be achieved by using readily available mechanical support devices, and the increasing acceptance of these devices as a bridge to transplant or even as destination treatment, probably contributed to the gradual decline of HHT procedures. Of importance, however, is the finding that the overall survival results of the HHT population in this study exceeded the results achieved by the REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) study (LVAD as destination treatment), which reports a 1-year survival of 52% with LVAD versus 84% in this HHT population [Rose 2001].

Although the results of this study demonstrate that HHT is a viable option in patients who do not qualify for standard OHT, this approach has a few disadvantages that are related to its nature. These disadvantages include the later recognition of rejection, difficulties in performing transvenous endomyocardial biopsies [Barnard1979], arrhythmia of the native heart [Alexopoulos 1988; Kotliar 1991; McMullan2003], native heart angina, thrombembolism with the need for permanent anticoagulation to prevent thrombi development in the poorly contracting and dilated native left ventricle [Tagusari 1999], valvular heart disease [Mangoush 2004], and compression of the right middle and lower lung lobe with lung atelectasis. Yet, there was no statistically significant difference between the groups' reported causes of death, which could possibly be related to the aforementioned shortcomings (e.g. cerebrovascular accidents, hemorrhage, pulmonary complications) (Table 2). The only significant difference that was found was a higher incidence of graft failure in the HHT group. Whether this is related to the later recognition of rejection episodes or possibly to the selection of marginal donor organs remains speculative.

In summary, HHT is nowadays rarely utilized in patients who do not qualify for standard OHT. Specific indications mainly include end-stage heart failure with persistent pulmonary hypertension and a significant donor–recipient size mismatch (>20%). With the advent of mechanical circulatory support devices, other options now exist to treat these patients and bridge individuals until OHT becomes feasible (normalization of pulmonary pressures) and a suitable donor organ becomes available. The results of this study, however, show that HHT remains a feasible and good option in a highly selected patient population, with overall good results.

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