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ORIGINAL ARTICLE

Better together: a reappraisal of heterotopic heart transplantation

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SUMMARY

Heterotopic heart transplantation (HHT) is rare in the modern era. When used as a biologic left ventricular assist, HHT provides pulsatile flow, supports the left ventricle with a physiologic cardiac output, responds to humoral stimuli, and with modern immunosuppression may offer long-term untethered survival. This study was undertaken to compare survival of HHT with orthotopic heart transplantation (OHT) to assess its viability in the modern era. In the United Network for Organ Sharing database, from January 1999 to December 2020, there were 27691 bicaval OHT, 13836 biatrial OHT, 1271 total OHT, and 51 HHT with sufficient follow-up. Survival was analyzed using restricted mean survival time (RMST) through 4 years as the outcome. In the first 4 years after transplant, compared with HHT, differences in RMST were 0.1 years (99% CI: −0.4 to 0.5 years) for bicaval OHT, 0.0 years (99% CI: −0.4 to 0.5 years) for biatrial OHT, and 0.0 years (99% CI: −0.5 to 0.4 years) for total OHT. In this cohort, survival was indistinguishable between HHT and OHT recipients in the first four years. Thus, HHT might be a viable alternative to durable mechanical circulatory assist particularly with size mismatched grafts or for patients with refractory pulmonary hypertension.

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Key words
biologic ventricular assist, cardiac transplantation, heterotopic, pulmonary hypertension, transplant survival

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Introduction

In 1967, Dr. Christiaan Barnard encountered early mortality in orthotopic cardiac transplant (OHT) recipients from acute rejection and graft failure. As well, acute right ventricular failure was observed in recipients with pre-existing pulmonary hypertension [1]. Barnard noted that heterotopic or "piggyback" transplantation could prevent this complication [2].

Barnard's technique for heterotopic heart transplantation (HHT) established the donor heart in parallel with the recipient heart (Fig. 1) [3,4]. The left and right atria

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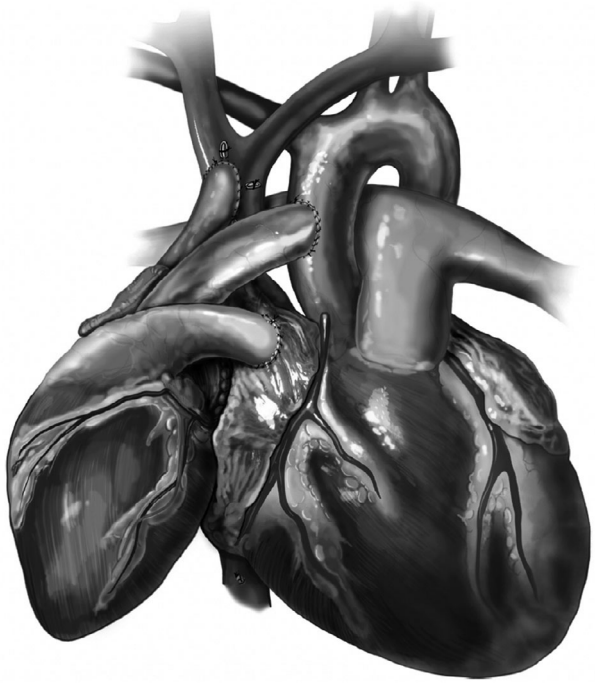

Figure 1 Heterotopic heart transplantation showing the smaller donor heart anastomosed to the recipient's native heart. Reprinted with permission from Copeland J, Copeland H. Heterotopic heart transplantation: technical considerations. Oper Tech Thorac Cardiovasc Surg. 2017; 21:269–280.

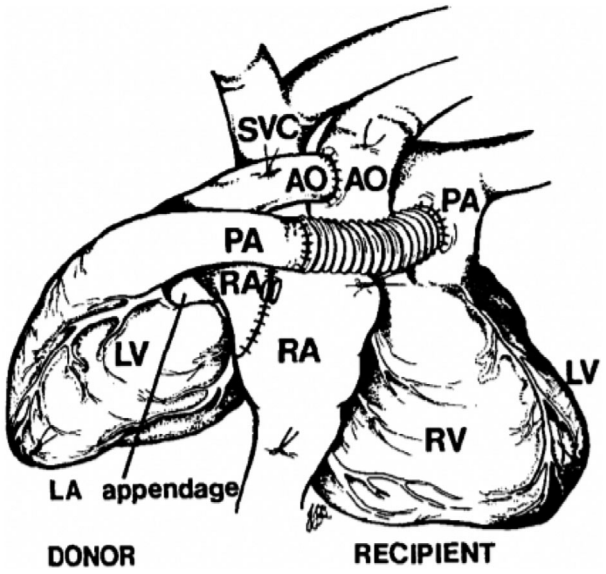

Figure 2 Heterotopic heart transplantation showing the use of a prosthetic end-to-side conduit to create a tension-free pulmonary artery anastomosis. Reprinted with permission from Novitzky D, Cooper DK, Barnard CN. The surgical technique of heterotopic heart transplantation. Ann Thorac Surg. 1983; 36(4): 476–482.

of the donor heart were anastomosed to the respective recipient chambers to create a biologic biventricular assist. Anastomoses were then made between the respective great vessels. A prosthetic end-to-side conduit was used to ensure a tension-free pulmonary artery anastomosis (Fig. 2) [5].

Barnard published a retrospective review of 40 patients who underwent HHT using this technique between 1974 and 1982, which demonstrated survival comparable to contemporary data from the Stanford group [6].

In a study of 42 consecutive heterotopic transplants from 1993 and 1999, Yacoub's group at Harefield Hospital found that there was no difference in 1-year survival between contemporary orthotopic recipients (74%) and heterotopic transplant recipients (81%) if donor body surface area (BSA) was at least 75% of recipient BSA [7]. This stands as the most contemporary comparison of the 2 techniques.

Despite these encouraging results, HHT was nearly forgotten [8,9]. Now, there are reasons to reconsider HHT in current surgical practice. Despite a shortage of donor hearts, nearly two-thirds of potential cardiac donors are declined because of allograft size, cold ischemic time, and donor-related pathology resulting in left ventricular ejection fraction (LVEF) less than 50% [8,10]. The average national waiting time for cardiac transplantation is more than 8 months in the United States [10]. HHT might be a viable option to increase the size of the donor pool and decrease time on the transplant waitlist [8,11]. Any donor heart in the LV assist position that could provide 5 l/min might be considered instead of a left ventricular assist device (LVAD). HHT, a biologic form of left ventricular support, might be used as a destination therapy, a long-term biologic support that could be replaced with an orthotopic transplant, or it could be removed in the event of recovery of left ventricular function [12]. Furthermore, if a recipient with severe, fixed pulmonary hypertension has preserved right ventricular function, HHT could eliminate the need for a mechanical LVAD and its associated complications.

This study evaluates 22 years of experience with HHT using the United Network for Organ Sharing (UNOS) database, which is a registry of all transplants performed in the United States since 1987. We hypothesize that HHT is associated with reasonable survival as compared with orthotopic heart transplantation.

Materials and methods

The UNOS database was used to select patients receiving first-time, solitary heart transplants from January 1999 to December 2020 with follow-up through June

Table 1. Select baseline donor, recipient, and transplant variables.

	Procedure			
	HHT *N* = 51	Bicaval OHT *N* = 27691	Biatrial OHT *N* = 13836	Total OHT (Bicaval, PV) *N* = 1271
Donor variables				
Male, *N* (%)	34 (66.7)	19123 (69.1)	9576 (69.2)	844 (66.4)
Race/Ethnicity, *N* (%)				
White/Caucasian	33 (64.7)	17784 (64.2)	9424 (68.1)	798 (62.8)
Black/African American	5 (9.8)	4556 (16.4)	1893 (13.7)	231 (18.2)
Hispanic	10 (19.6)	4532 (16.4)	2099 (15.2)	210 (16.5)
Other	3 (5.9)	819 (3.0)	420 (3.0)	32 (2.5)
Age, median (IQR), y	25 (18–32)	27 (19–39)	26 (18–39)	25 (16–38)
Ejection fraction*, median (IQR), %	60 (51–65)	60 (55–65)	60 (57–66)	60 (55–65)
Ischemic time†, median (IQR), h	3.5 (2.5–4.3)	3.2 (2.5–3.9)	3.2 (2.5–3.9)	3.4 (2.6–4.0)
Blood Group, *N* (%)				
A	18 (35.3)	9756 (35.2)	5060 (36.6)	450 (35.4)
B	5 (9.8)	3028 (10.9)	1362 (9.8)	117 (9.2)
AB	1 (2.0)	604 (2.2)	279 (2.0)	20 (1.6)
O	27 (52.9)	14303 (51.7)	7135 (51.6)	684 (53.8)
PHM Ratio Group, *N* (%)				
Severely undersized/septile 1	11 (21.6)	3555 (12.8)	1879 (13.6)	202 (15.9)
Moderate undersized/septile 2	5 (9.8)	3352 (12.1)	1609 (11.6)	118 (9.3)
Mildly undersized/septile 3	5 (9.8)	3309 (11.9)	1530 (11.1)	114 (9.0)
Matched/septile 4	8 (15.7)	3253 (11.8)	1634 (11.8)	114 (9.0)
Mildly oversized/septile 5	3 (5.9)	3313 (12.0)	1615 (11.7)	119 (9.4)
Moderate oversized/septile 6	0 (0.0)	3299 (11.9)	1526 (11.0)	126 (9.9)
Severely oversized/septile 7	7 (13.7)	3289 (11.9)	1603 (11.6)	137 (10.8)
N/A or Unknown	12 (23.5)	4321 (15.6)	2440 (17.6)	341 (26.8)
Recipient variables				
Male, *N* (%)	32(62.7)	19965 (72.1)	10058 (72.7)	889 (69.9)
Race/Ethnicity, *N* (%)				
White/Caucasian	34 (66.7)	18351 (66.3)	9870 (71.3)	823 (64.8)
Black/African American	9 (17.6)	5514 (19.9)	2244 (16.2)	284 (22.3)
Hispanic	7 (13.7)	2530 (9.1)	1201 (8.7)	97 (7.6)
Other/Unknown	1 (2.0)	1296 (4.7)	521 (3.8)	67 (5.3)
Age, median (IQR), y	52 (34–58)	53 (37–61)	53 (37–60)	50 (18–59)
Blood Group				
A	19 (37.3)	11117 (40.2)	5819 (42.1)	536 (42.2)
B	7 (13.7)	4046 (14.6)	1832 (13.2)	167 (13.1)
AB	2 (3.9)	1448 (5.2)	726 (5.2)	63 (5.0)
O	23 (45.1)	11080 (40.0)	5459 (39.5)	505 (39.7)
Diagnosis of dilated myopathy	38 (74.5)	21662 (78.2)	10741 (77.6)	948 (74.6)
PA mean pressure‡, mm Hg	25.0 (19.0–34.0)	27.0 (20.0–34.0)	27.0 (20.0–35.0)	25.0 (19.0–32.0)
TPG§, median (IQR), mm Hg	10.0 (7.5–13.0)	9.0 (6.0–12.0)	9 (6.0–12.0)	9.0 (6.0–12.0)
PVR¶, Wood units	2.1 (1.6–3.6)	2.1 (1.4–3.1)	2.1 (1.4–3.1)	2.0 (1.3–3.0)
Creatinine**, median (IQR), mg/dL	1.4 (1.0–1.8)	1.1 (0.8–1.4)	1.1 (0.9–1.4)	1.1 (0.7–1.4)
Bilirubin††, median (IQR), mg/dL	0.8 (0.5–1.2)	0.7 (0.5–1.2)	0.8 (0.5–1.3)	0.7 (0.5–1.2)
Days on waitlist, median (IQR)	171 (55–472)	80 (24–232)	86 (26–244)	64 (22–189)
Waitlist status at tx, *N* (%)				
1A	19 (37.2)	15670 (56.6)	6839 (49.4)	731 (57.5)
1B	18 (35.3)	8769 (31.7)	4527 (32.7)	376 (29.6)
2	14 (27.5)	2754 (9.9)	2383 (17.2)	154 (12.1)
New Status 1	0 (0.0)	44 (0.2)	7 (<0.1)	2 (0.2)
New Status 2	0 (0.0)	225 (0.8)	41 (0.3)	3 (0.2)
New Status 3	0 (0.0)	109 (0.4)	23 (0.2)	5 (0.4)
New Status 4	0 (0.0)	98 (0.3)	13 (0.1)	0 (0.0)

Transplant International 2021; 34: 2184–2191

Table 1. Continued.

	Procedure			
	HHT *N* = 51	Bicaval OHT *N* = 27691	Biatrial OHT *N* = 13836	Total OHT (Bicaval, PV) *N* = 1271
New Status 5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
New Status 6	0 (0.0)	22 (0.1)	3 (<0.1)	0 (0.0)
IABP at tx, *N* (%)	1 (2.0)	1573 (5.7)	617 (4.5)	84 (6.6)
VA-ECMO at tx, *N* (%)	0 (0.0)	364 (1.3)	175 (1.3)	21 (1.7)
VAD Device at tx, *N* (%)				
None	12 (23.5)	15760 (56.9)	6236 (45.1)	701 (55.1)
LVAD	7 (13.7)	8093 (29.2)	2270 (16.4)	237 (18.7)
RVAD	0 (0)	60 (0.2)	22 (0.2)	3 (0.2)
TAH	0 (0)	180 (0.7)	141 (1.0)	4 (0.3)
BIVAD	2 (3.9)	735 (2.6)	230 (1.7)	34 (2.7)
Device Unspecified	1 (2.0)	743 (2.7)	997 (7.2)	61 (4.8)
Unknown	29 (56.9)	2120 (7.7)	3940 (28.5)	231 (18.2)

Based on OPTN data as of June 30, 2021.

HHT, heterotopic heart transplantation; OHT, orthotopic heart transplantation; IQR, interquartile range; PHM, predicted heart mass; y, year; tx, transplant; rv, right ventricular; PA, pulmonary artery; TPG, trans-pulmonary gradient; PVR, pulmonary vascular resistance; LVAD, left ventricular assist device; RVAD, right ventricular assist device; TAH, total artificial heart; BIVAD, biventricular ventricular assist device; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

*Fifteen HHT, 757 bicaval OHT, 1555 biatrial OHT, and 112 total OHT were missing ejection fraction.

†Sixteen HHT, 685 bicaval OHT, 875 biatrial OHT, and 52 total OHT were missing ischemic time.

‡Five HHT, 2762 bicaval OHT, 1973 biatrial OHT, and 186 total OHT were missing mean pulmonary artery pressure.

§Seven HHT, 5061 bicaval OHT, 3186 biatrial OHT, and 290 total OHT were missing trans-pulmonary gradient.

¶Fourteen HHT, 6108 bicaval OHT, 3850 biatrial OHT, and 364 total OHT were missing pulmonary vascular resistance.

**Two HHT, 206 bicaval OHT, 369 biatrial OHT, and 13 total OHT were missing recipient creatinine at transplant.

††Six HHT, 636 bicaval OHT, 812 biatrial OHT, and 64 total OHT were missing recipient total bilirubin at transplant.

30, 2021. After exclusions for multi-organ transplant, re-transplantation, and recipients transplanted after 2017 who were still alive with a functioning allograft (due to insufficient follow-up), the analysis cohort consisted of 42849 patients who received heart transplants. Of these transplants, 27691 were bicaval OHT (i.e., anastomosis performed with donor to recipient superior vena cava and inferior vena cava), 13836 were biatrial OHT (i.e., anastomosis performed with donor to recipient left and right atria), 1271 were total OHT (i.e., orthotopic with bicaval and pulmonary venous anastomoses), and 51 were HHT.

Statistical analysis

In addition to standard descriptive statistics, the Kaplan-Meier (KM) method [13] was used to obtain survival estimates for each type of heart transplant. The primary outcome was restricted mean survival time (RMST) through 4 years. The restricted mean survival time with landmark time τ is defined as the area under the survival curve up to τ and represents the time lived in the first τ time units [14]. Thus, the difference in RMST through 4 years post-transplant was calculated as the difference in the areas under the survival curves. RMST accounts for the entire survival trajectory through the chosen time horizon as opposed to a single time point and produces treatment/exposure differences in units of time, which are more meaningful, readily understood, and actionable than abstract survival probabilities or especially hazard ratios. For this analysis, an event was defined as patient mortality or allograft failure. The data were prepared using SAS version 9.4 (SAS Institute, Cary, NC) and analyzed using R version 4.0.4 [15] with the survival [16,17], survRM2 [18], and jskm [19] packages.

Results

A plot of number of heterotopic procedures by transplant year is provided in Fig. S1, showing a spike in heterotopic transplants performed in 2017 ($n = 8$). In the timeframe considered for this study, the only year

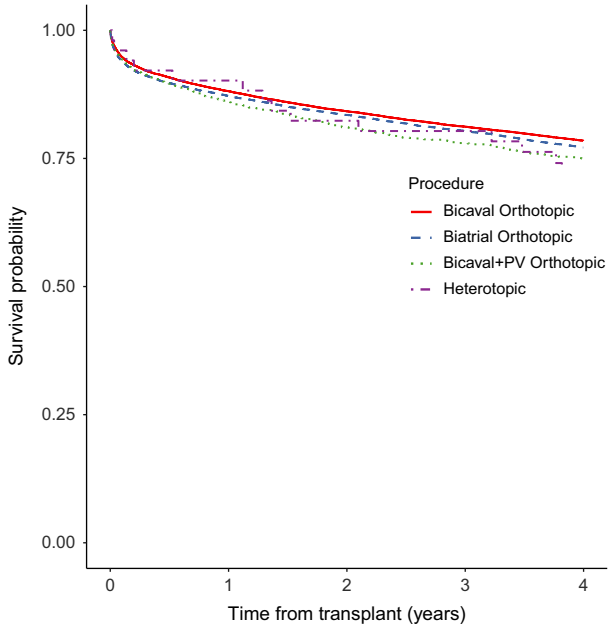

Figure 3 Kaplan-Meier survival curves for recipient by heart transplant procedure type. Based on OPTN data as of June 30, 2021. Patients at risk across time are listed in Table 2. *PV*, pulmonary venous.

with more heterotopic procedures performed was 1999 (n = 17).

During a median follow-up time of 6.6 years, 19495 (45.5%) deaths and/or graft failures occurred among the 42849 recipients who were transplanted starting in 1999. Of these 19495 events, 9339 occurred within the first four years after transplant. Most heart transplant recipients were male, Caucasian, 50 years or older at the time of transplant, blood type O or A, and were diagnosed with dilated cardiomyopathy across all groups. The donor-recipient predicted heart mass ratio was determined by predicted heart mass equations (for donors and recipients at least 16 years of age), and the results were divided into septiles ranging from severely undersized to severely oversized [20]. Of note, a plurality (n = 21, 41.2%) of the 51 heterotopic heart transplantation allografts were undersized (septiles 1, 2, or 3), with half of those being severely undersized (septile 1). Additionally, the 51 patients who underwent heterotopic transplantation spent a longer time on the waitlist: median 171 days (IQR: 55 to 472), and UNOS Status 1A was the most common (n = 19, 37.3%) waitlist designation at the time of transplantation among the heterotopic cohort (Table 1).

Kaplan-Meier (KM) survival curves are displayed in Fig. 3 and an extended risk table [21] is provided in Table 2. Using HHT recipients as the comparator for survival, in the first 4 years after transplant estimated differences in RMST were 0.1 years (99% CI: −0.4 to 0.5 years) for bicaval OHT recipients; 0.0 years (99% CI: −0.4 to 0.5 years) for biatrial OHT recipients; and 0.0 years (99% CI: −0.5 to 0.4 years) for total OHT

Table 2. Extended risk table through τ = 4 years after transplant.

	Time from transplant (years)				
	0	1	2	3	4
Bicaval OHT					
At risk	27 588	24 275	23 079	21 502	19 020
Censored	0	132	248	1012	2791
Events	103	3284	4364	5177	5880
Biatrial OHT					
At risk	13 799	11 972	11 373	10 731	9907
Censored	0	96	187	403	805
Events	37	1768	2276	2702	3124
Bicaval+PV OHT					
At risk	1266	1085	1009	949	862
Censored	0	11	23	45	96
Events	5	175	239	277	313
HHT					
At risk	51	46	42	40	30
Censored	0	0	0	1	6
Events	0	5	9	10	15

Based on OPTN data as of June 30, 2021.

OHT, orthotopic heart transplantation; PV, pulmonary venous; HHT, heterotopic heart transplantation.

recipients, where positive differences correspond to more days lived and negative differences to fewer days lived. Thus, the survival of HHT recipients is indistinguishable from OHT recipients in the first four years after transplant.

Discussion

Our study demonstrates that a small number of HHT recipients had a 4-year survival essentially identical to OHT recipients. This data supports the plausibility of use of HHT as a biologic left ventricular assist in recipients with preserved right ventricular function. The size match criteria, degree of acceptable donor heart dysfunction, and ischemic time limitations remain to be further defined. Cautious use of this technique could potentially help expand the donor pool, decrease LVAD implantations and in turn minimize the inherent risk of LVAD sequela, as well as reduce costs, morbidity, and mortality from multiple procedures. Studies of this procedure in previous eras are mostly supportive but not definitive (Table S1).

Routine angiographic and histologic evaluations have been reported in heterotopic cardiac grafts. Biopsy via right internal jugular approach is facilitated by placing hemostatic clips at the uppermost point of the donor-recipient superior vena cava anastomosis. This enables fluoroscopic localization [22,23]. Standard right internal jugular vein approach can be safely performed to assess right heart pressures and to take endomyocardial tissue samples [23].

OPTN/UNOS implications

The current strict monitoring of allograft one-year outcome has a stifling effect on innovation, particularly in smaller programs. We believe that HHT should be analyzed separately from OHT much as combined heart and other organ transplants are evaluated. This would not penalize programs for appropriate risk taking that may well expand the donor pool. In view of the data presented, HHT would appear to be an acceptable risk when compared with OHT.

Alternate applications

LVADs have been a remarkable advance for patients, and survival has improved tremendously with the current generation of continuous flow centrifugal devices. However, the lack of pulsatility is associated with an induced deficiency in von Willebrand factor and resultant arteriovenous malformations, mucosal bleeds, strokes, aortic insufficiency, hypertension, and other adverse events relating to the device itself. In addition, patients with late right ventricular failure following permanent LVAD might be candidates for HHT, if OHT is not felt to be appropriate. Given the potential availability of HHT grafts, this may represent an option for these patients who are not well served by current treatments.

Limitations

This study is limited by both its observational study design and the lack of follow-up beyond 4 years for 7 of the 9 HHT recipients who were transplanted starting in 2017 and were alive with a functioning allograft as of June 2021. Moreover, as there were only 51 single heterotopic heart transplants that occurred during the entire study period, the potential for bias in the estimated differences is more pronounced. Finally, this was an unadjusted analysis and does not account for possible differences in survival due to confounding variables.

Conclusion

Few papers have been published on the short- or long-term results of HHT. The current body of literature is comprised of small, single-center studies [22–25]. The most impressive was the report from Harefield Hospital on nearly as many patients as in this report showing no difference in 1-year survival between orthotopic and heterotopic transplants [7].

This is the first analysis of HHT outcomes based on a national registry over 22 years. Data from the UNOS database suggest that HHT recipients have essentially identical survival to OHT recipients in the first four years. Hence, HHT might possibly be used to expand the donor pool. HHT offers patients an additional option for transplantation that could potentially utilize smaller, good quality donor hearts, without sacrificing transplant survival.

Authorship

Hannah Cockrell and Kristen Carter: substantial contributions to data acquisition, analysis and interpretation as well as substantial contributions to the drafting of the work. Robert O'Brien: substantial contributions to the acquisition, preparation, analysis and interpretation of data and writing the statistical content. Taylor B. Shaw: substantial contributions to data acquisition and analysis. David A. Baran: substantial contributions to data analysis, interpretation and revision of the

manuscript. Matthew E. Kutcher: assisted with revision of the manuscript. Jack G. Copeland and Hannah Copeland: made substantial contributions to the conception of the work, design of the study, acquisition, analysis and interpretation of the data, drafting of the work, and revisions of the manuscript.

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Conflict of interest

Dr. David Baran has received consulting fees from Getinge, Livanova, Abiomed, and MC3, honoraria from Novartis and Pfizer, and research support paid to Sentara Heart Hospital from Abbott. Dr. Jack Copeland is a consultant for Syncardia total artificial heart system. Dr. Hannah Copeland is a consultant for Abbott and Paragonix Technologies.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Published results with heterotopic heart transplantation in the past three decades.

Figure S1. Number of heterotopic heart transplants by year.

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