Long-term transplant outcomes of donor hearts with left ventricular dysfunction

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ABSTRACT

Objective: Despite small single-center reports demonstrating acceptable outcomes using donor hearts with left ventricular dysfunction, 19% of potential donor hearts are currently unused exclusively because of left ventricular dysfunction. We investigated modern long-term survival of transplanted donor hearts with left ventricular dysfunction using a large, diverse cohort.

Methods: Using the United Network for Organ Sharing database, we reviewed all adult heart transplants between January 2000 and March 2016. Baseline and post-operative characteristics and Kaplan–Meier survival curves were compared. A covariates-adjusted Cox regression model was developed to estimate post-transplant mortality. To address observed variation in patient profile across donor ejection fraction, a propensity score was built using Cox predictors as covariates in a generalized multiple linear regression model. All the variables in the original Cox model were included. For each recipient, a predicted donor ejection fraction was generated and exported as a new balancing score that was used in a subsequent Cox model. Cubic spline analysis suggested that at most 3 and perhaps no ejection fraction categories were appropriate. Therefore, in 1 Cox model we added donor ejection fraction as a grouped variable (using the spline-directed categories) and in the other as a continuous variable.

Results: A total of 31,712 donor hearts were transplanted during the study period. A total of 742 donor hearts were excluded for no recorded left ventricular ejection fraction, and 20 donor hearts were excluded for left ventricular ejection fraction less than 20%. Donor hearts with reduced left ventricular ejection fraction were from younger donors, more commonly male donors, and donors with lower body mass index than normal donor hearts. Recipients of donor hearts with reduced left ventricular ejection fraction were more likely to be on mechanical ventilation. Kaplan–Meier curves revealed no significant differences in recipient survival up to 15 years of follow-up ($P = .694$ log-rank test). Cox regression analysis showed that after adjustment for propensity variation, transplant year, and region, ejection fraction had no statistically significant impact on mortality when analyzed as a categoric or continuous variable. Left ventricular ejection fraction at approximately 1 year after transplantation was normal for all groups.

Conclusions: Carefully selected donor hearts with even markedly diminished left ventricular ejection fraction can be transplanted with long-term survival equivalent to normal donor hearts and therefore should not be excluded from

No statistically significant differences in Kaplan–Meier survival curves were found among groups stratified by LVEF.

Central Message

Hearts with diminished LVEF should not be excluded from consideration of transplantation on the basis of depressed LV function alone.

Perspective

Despite evidence that approximately 20% of donor hearts are not used for transplantation exclusively because of depressed LV function, our study finds that donor hearts with even markedly diminished LV function may be transplanted with long-term survival equivalent to hearts with normal LV function.

See Commentaries on pages 1876, 1878, and 1880.

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Abbreviations and Acronyms

EF	= ejection fraction
LV	= left ventricular
LVEF	= left ventricular ejection fraction
UNOS	= United Network for Organ Sharing

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consideration on the basis of depressed left ventricular ejection fraction alone. Functional recovery of even the most impaired donor hearts in this study suggests that studies of left ventricular function in the setting of brain death should be interpreted cautiously. (*J Thorac Cardiovasc Surg* 2019;157:1865-75)

Transplant rates have remained static over the past 15 years at approximately 2000 per year in the United States,¹ and donor use rates are trending downward.² This has provoked recent reexamination of donor hearts previously excluded from consideration, including use of hearts with a history of resuscitated cardiac arrest^{3,4} and hearts from older

donors.⁵ We sought to examine another source of underused donor hearts: those with diminished left ventricular (LV) function. Among the reasons that hearts are declined for transplantation, ventricular dysfunction (often a sequel of the pathophysiologic environment caused by brain death) is among the most common and potentially tractable. Previous work from our group has documented that 19% of potential donor hearts (>1300 hearts per year) are not accepted for transplantation based entirely on LV dysfunction without evidence of structural disease.⁶ This figure has not been affected by somewhat small, mostly single-center clinical studies⁷⁻⁹ demonstrating equivalent short- and medium-term outcomes of dysfunctional donor hearts when compared with donor hearts with normal LV function or by experimental studies demonstrating functional resuscitation of hearts damaged by the pathophysiology of brain death.^{10,11} Brain death has been associated not only with impaired donor organ function, an effect that is pronounced in the heart, but also with postoperative complications, including primary graft dysfunction, increased immunogenicity resulting in a higher incidence of both acute and chronic rejection, and worse long-term outcomes.^{12,13} The mechanism of brain death–induced ventricular dysfunction is not well understood and likely multifactorial. Ischemic injury,¹⁴ direct catecholamine or cytokine-induced myocardial injury,^{11,15} and impaired β -adrenergic receptor signaling¹⁶ have all been implicated. Although both regional and global LV dysfunction are common in the setting of brain death, neither is correlated with pathologic changes, indicating that the dysfunction is

FIGURE 1. Univariate, restricted cubic spline regression using a least-squares model between donor LVEF and survival. LV, Left ventricular.

TABLE 1. Comparison of baseline heart donor characteristics

	Group 1 (n = 124)	Group 2 (n = 9203)	Group 3 (n = 21,623)	P value
Age*	21.0 (13.0, 17.0, 28.0, 43.0)	28.0 (16.0, 21.0, 39.0, 52.0)	30.0 (16.0, 22.0, 42.0, 53.0)	<.001
Gender (%)				<.001
Male	76.6	73.2	69.8	
Female	23.4	26.8	30.2	
Race (%)				
White	75.0	66.7	66.6	.002
Black	16.1	15.3	14.1	
Hispanic	8.87	15.3	16.2	
Asian	0.00	1.31	1.82	
Indigenous†	0.00	0.61	0.69	
Multiracial	0.00	0.67	0.57	
Unknown	0.00	0.05	0.01	
Body mass index‡	23.7 (18.3, 21.6, 26.8, 33.5)	25.4 (19.6, 22.7, 29.1, 36.7)	26.0 (19.7, 23.1, 29.8, 37.7)	<.001
Cause of death (%)				
Anoxia	19.4	17.3	16.2	<.001
Stroke	12.9	20.7	24.5	
Head trauma	66.1	59.3	56.5	
Brain tumor	0.00	0.68	0.86	
Other	1.61	2.08	1.88	
Inotropes at procurement (%)	51.7	53.5	51.8	.091
Triiodothyronine at procurement	4.03	1.96	1.40	<.001
Ischemic time§	3.23 (1.55, 2.47, 3.77, 4.60)	3.13 (1.53, 2.42, 3.82, 4.85)	3.20 (1.57, 2.48, 3.87, 4.95)	.211
LVEF	33.0 (19.0, 30.0, 35.0, 37.0)	55.0 (45.0, 51.0, 55.0, 58.0)	65.0 (60.0, 60.0, 70.0, 75.0)	<.001

LVEF, Left ventricular ejection fraction. *Age is reported as median years with 5th, 25th, 75th, and 95th percentiles. †American Indian, Alaska Native, or Native Hawaiian/Other Pacific Islander. ‡Body mass index is reported as median kg/m² with 5th, 25th, 75th, and 95th percentiles. §Ischemic time is reported as median hours with 5th, 25th, 75th, and 95th percentiles. ||LVEF is reported as median % with 5th, 25th, 75th, and 95th percentiles.

irreversible.^{17,18} Given the experimental and available clinical evidence supporting the possibility of functional resuscitation of donor hearts with impaired ventricular function in the context of brain death, we believed further investigation was warranted. The current study is an effort to provide more long-term outcome data of donor hearts with LV dysfunction in the modern era of heart transplantation and determine whether consideration of expansion of the donor pool to include some of these organs is appropriate.

MATERIALS AND METHODS

Our study design was submitted to the Institutional Review Board at Loma Linda University Medical Center, which determined that the study did not meet the definition of human subject research because it did not involve identifiable information, no data or specimens were collected, and there was no direct intervention or interaction. Therefore, the Institutional Review Board decided our study did not require review or approval.

All isolated, adult (recipient aged ≥ 18 years), first-time heart transplants in the United States between January 1, 2000, and March 31, 2016, were analyzed. Data on donor hearts and post-transplant outcomes were obtained from the United Network for Organ Sharing (UNOS) as the contractor for the Organ Procurement and Transplantation Network provided by way of Standard Transplant Analysis and Research files. Hearts that were transplanted in conjunction with other organs were excluded from this analysis. This work was supported in part by Health

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Donor hearts with left ventricular ejection fraction (LVEF) less than 20% were excluded from the study because we found the values to be implausible. Donor hearts without recorded LVEF were also excluded. The overwhelming majority of LVEF calculations were made by echocardiogram (95.1%), although left ventriculogram during left heart catheterization was used in 2.5% of cases and multi-gated acquisition scan was used in 0.03%. Baseline characteristics of both donor hearts and recipients were compared, as were recipient postoperative complications and overall survival.

Statistical Analysis

All data were analyzed with SAS 9.4 (SAS Institute Inc, Cary, NC). Kolmogorov–Smirnov analysis demonstrated that continuous variables were not normally distributed; therefore, data are reported as median with selected percentiles (5th, 25th, 75th, and 95th) above and below the median and compared using the Kruskal–Wallis test. The chi-square test was used to compare categorical variables. All reported *P* values were 2 sided. A univariate, restricted, cubic spline regression was performed using a least-squares model between donor LVEF and survival. We based the smoother on a restricted spline basis with 5 equal knots placed at the 1/6, 2/6, 3/6, 4/6, and 5/6 quantiles. Knots 1 to 5 corresponded with the following donor ejection fractions (EFs): 17.33%, 33.67%, 50.0%, 66.33%, and 82.67%, respectively. This model indicates a statistically

TABLE 2. Comparison of baseline heart recipient characteristics

	Group 1 (n = 124)	Group 2 (n = 9203)	Group 3 (n = 21,623)	P value
Baseline				
Age*	54.5 (25.0, 44.5, 62.0, 67.0)	55.0 (26.0, 46.0, 62.0, 68.0)	55.0 (26.0, 46.0, 62.0, 68.0)	.556
Gender (%)				.341
Male	74.2	75.8	74.8	
Female	25.8	24.2	25.2	
Race (%)				
White	71.8	70.6	70.2	.006
Black	16.1	19.2	17.9	
Hispanic	10.5	6.6	7.8	
Asian	1.61	2.54	2.88	
Indigenous	0.00	0.52	0.71	
Multiracial	0.00	0.48	0.52	
Body mass index†	26.5 (18.6, 22.7, 29.5, 33.2)	26.5 (19.5, 23.4, 29.9, 35.3)	26.6 (19.5, 23.4, 30.2, 35.3)	.983
Ventilator‡	4.03	1.52	1.64	<.001
ECMO‡	0.81	0.55	.59	.681
LVAD‡	9.21	13.5	14.0	.115
Inotropes‡	54.7	43.5	41.7	<.001
Total days on waiting list§	81.5 (4, 22.5, 232.5, 810)	89 (4, 26, 251, 830)	89 (4, 27, 252, 853)	.024
Days status 1A§	15 (1, 6, 35, 107)	21 (0, 0, 28, 98)	21 (2, 8, 40, 133)	.441
Days status 1B§	22.5 (2, 7, 96, 282)	49 (2, 13, 136, 419)	48 (2, 13, 132, 411)	.011
Days status 2§	115 (1.5, 25, 408, 916)	95 (3, 27, 287, 940)	96 (3, 26, 287, 928)	.009
Postoperative				
ECMO at 72 h (%)	0.81	0.55	0.59	.681
Length of stay§	13 (7, 10, 24, 83)	14 (7, 10, 22, 53)	14 (7, 10, 21, 53)	<.001
New dialysis (%)	9.68	10.35	10.19	<.001
Pacemaker (%)	3.23	3.10	3.50	<.001
New stroke (%)	0.00	2.48	2.39	<.001
Treated for rejection in 1 y (%)	20.16	19.88	19.76	<.001
LVEF at 1 y	60 (45, 55, 64, 70)	60 (45, 55, 65, 70)	60 (50, 55, 65, 71)	<.001

ECMO, Extracorporeal membrane oxygenation; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction. *Age is reported as median years with 5th, 25th, 75th, and 95th percentiles. †Body mass index is reported as median kg/m² with 5th, 25th, 75th, and 95th percentiles. ‡At time of transplant (%). §Median days with 5th, 25th, 75th, and 95th percentiles. ||LVEF reported as median percent with 5th, 25th, 75th, and 95th percentiles.

significant fit ($F = 22.60$, $P < .0001$) with Knot 5 being statistically different from Knot 2 ($P = .011$), Knot 3 ($P = .006$), and Knot 4 ($P = .040$). Knot 1 was not identified as being statistically different from Knot 5 ($P = .269$). Because of the appearance of the cubic spline curve (Figure 1), we thought that at most 3 groups (group 1: EF <40, group 2: EF 40–≤60, and group 3: EF >60) and perhaps no groups would be most appropriate.

Kaplan–Meier curves with donor hearts grouped by LV function, as indicated by the spine analysis, were generated to compare the overall survival of the groups. Given the imbalance in sample number and resultant events among the groups, Kaplan–Meier curves were truncated for less than 10 patients at risk in an attempt to attenuate wide confidence intervals.

A covariates-adjusted Cox regression model with robust standard errors was developed to estimate post-transplant mortality hazard ratios with 95% confidence interval for LV dysfunction. Covariates considered for inclusion in the model included all available donor and recipient data (Tables 1 and 2), as well as UNOS region and transplant era (we divided the 17 years of the study into 4 different periods: 2000–2003, 2004–2007, 2008–2011, and 2012–2016). The Cox model assumes that hazard ratios should be constant over time (proportional hazards). We assessed each categorical covariate for whether the assumption of proportional hazards was reasonable. Where nonproportional hazards were present, we considered a stratified model. We assessed proportional hazards with a plot of standardized score

residuals over time. We concluded that if the residuals were unusually large at any time point, the proportional hazards assumption was violated. In that case, we produced plots of randomly generated score processes to allow for graphic assessment of the observed residuals. To address observed variation in patient profile across donor EF, a propensity score was built using Cox predictors as covariates in a generalized multiple linear regression model.¹⁹ All the variables in the original Cox model were included. For each recipient, a predicted donor EF was generated and exported as a new balancing score that was used in a subsequent Cox model. As noted earlier, Cubic spline analysis suggested that at most 3 groups and perhaps no groups were appropriate. We evaluated donor EF separately as a grouped variable and then as a continuous variable in the Cox model.

RESULTS

During the study period, 31,712 isolated, first-time heart transplants were performed in recipients older than 18 years of age. Of these, 124 were in group 1 (EF <40%), 9203 were in group 2 (EF 40%–59.9%), and 21,623 were in group 3 (≥60%). Median LVEF for groups 1 to 3 was 33.0%, 55.0%, and 65.0%, respectively ($P < .001$). A total of 742 donor hearts were excluded for not having a recorded

FIGURE 2. Kaplan–Meier survival curves with 95% Hall–Wellner bands. No significant differences in post-transplant Kaplan–Meier survival curves were found among groups stratified by LVEF. LVEF less than 40% blue, LVEF 40% to 59.9% red, LVEF 60% or greater green. *EF*, Ejection fraction.

LVEF, and 20 donor hearts were excluded because of LVEF less than 20%. Mean follow-up was 1890 ± 1564 (standard deviation) days.

Comparison of baseline heart donor characteristics is shown in Table 1. Median age varied inversely with ventricular function, and differences were statistically significant

($P < .001$). Group 3 had the highest proportion of female donors (30.2%), and group 1 had the lowest (23.4%) ($P < .001$). Donors in group 1 were significantly more likely to be white ($P = .002$). Group 1 had the lowest median body mass index at 23.7 kg/m^2 , whereas group 3 had the highest at 26.0 kg/m^2 ($P < .001$). Donors in group 1 were more likely to have died of anoxia and head trauma and less likely to have died of stroke ($P < .001$). They were also more likely to be on triiodothyronine at the time of procurement. Comparison of recipient characteristics is shown in Table 2. There were no statistically significant differences in median age, gender, median body mass index, or use of mechanical circulatory support before transplant. Recipients of donor hearts from group 1 were significantly more likely to be on ventilator and inotropic support at the time of transplant.

Kaplan–Meier survival curves demonstrated no statistically significant differences in survival among the 3 groups at up to 15 years of follow-up ($P = .694$) (Figure 2). There were no significant differences in the need for extracorporeal membrane oxygenation at 72 hours after transplant, and differences in length of stay, new indication for dialysis, new pacemaker, and treatment for rejection within 1 year of transplant were not clinically significant. Differences in LVEF at approximately 1 year after transplantation were statistically but

TABLE 3. Hearts transplanted in each left ventricular ejection fraction group by United Network for Organ Sharing region

	Group 1	Group 2	Group 3	<i>P</i> value
UNOS region (% of total transplants performed)				<.001
1 (3.8%)	12 (1.0%)	384 (32.2%)	778 (65.3%)	
2 (13.3%)	24 (0.57%)	1348 (32.1%)	2680 (63.7%)	
3 (12.1%)	5 (0.13%)	1105 (28.9%)	2652 (69.4%)	
4 (10.7%)	10 (0.29%)	979 (28.8%)	2392 (70.3%)	
5 (15.8%)	16 (0.32%)	1031 (20.6%)	3923 (78.2%)	
6 (3.0%)	0 (0.0%)	193 (20.0%)	761 (79.0%)	
7 (9.3%)	11 (0.37%)	797 (27.1%)	1905 (64.8%)	
8 (5.5%)	3 (0.17%)	483 (27.5%)	1256 (71.4%)	
9 (6.7%)	14 (0.66%)	739 (34.9%)	1297 (61.2%)	
10 (8.7%)	13 (0.47%)	877 (31.9%)	1791 (65.2%)	
11 (11.2%)	16 (0.45%)	1285 (36.0%)	2213 (62.1%)	

UNOS, United Network for Organ Sharing.

TABLE 4. Cox regression hazard ratios and confidence intervals using left ventricular ejection fraction as a categorical variable

Parameter	Parameter estimate	Standard error	Chi-square	P value	HR	95% Wald confidence limits
Group 2 (EF 40%-59.9%)	0.091	0.295	0.095	.758	1.095*	0.615-1.951
Group 1 (EF <40%)	0.031	0.052	0.353	.553	1.031*	0.932-1.142
Age recipient	0.015	0.002	64.45	<.001	1.015†	1.011-1.019
Age donor	0.003	0.002	2.491	.115	1.003†	0.999-1.007
Female gender	0.027	0.053	0.250	.617	1.027	0.925-1.140
Race/ethnicity recipient						
Black	0.096	0.055	2.996	.084	1.101‡	0.987-1.227
Hispanic	0.013	0.095	0.019	.892	1.013‡	0.841-1.220
Asian	0.335	0.186	3.256	.071	1.399‡	0.971-2.013
American Indian	−0.067	0.417	0.026	.873	0.935‡	0.413-2.117
Native Hawaiian	−0.428	0.344	1.543	.214	0.652‡	0.332-1.280
Multiracial	0.021	0.295	0.005	.944	1.021‡	0.573-1.818
Race/ethnicity donor						
Black	0.061	0.067	0.821	.365	1.063‡	0.932-1.212
Hispanic	0.096	0.072	1.763	.184	1.101‡	0.955-1.268
Asian	0.367	0.213	2.963	.085	1.443‡	0.950-2.192
American Indian	−0.447	0.308	2.105	.147	0.640‡	0.350-1.170
Native Hawaiian	−0.334	0.715	0.219	.640	0.716‡	0.176-2.908
Multiracial	0.164	0.325	0.254	.614	1.178‡	0.623-2.229
BMI recipient	0.009	0.005	3.375	.066	1.009	0.999-1.018
Days on wait list	0.000	0.000	0.045	.833	1.000	1.000-1.000
UNOS region						
1	0.759	0.243	9.761	.002	2.135§	1.327-3.437
2	0.627	0.204	9.412	.002	1.873§	1.254-2.796
3	0.557	0.197	7.946	.005	1.745§	1.185-2.569
4	0.429	0.187	5.281	.022	1.536§	1.065-2.215
5	0.038	0.174	0.048	.827	1.039§	1.739-1.461
7	0.572	0.203	7.983	.005	1.772§	1.192-2.636
8	0.509	0.196	6.737	.009	1.664§	1.133-2.445
9	0.681	0.220	9.585	.002	1.976§	1.284-3.041
10	0.780	0.220	12.54	<.001	2.182§	1.417-3.360
11	1.098	0.225	23.81	<.001	2.998§	1.929-4.660
Era						
2000-2003	0.16909	0.03706	20.814	<.001	1.184	1.101-1.273
2004-2007	0.13619	0.03705	13.508	.0002	1.146	1.066-1.232
2008-2011	0.03944	0.03818	1.0668	.3017	1.040	0.965-1.121
Propensity score	0.154	0.034	19.97	<.001	1.166¶	1.090-1.248
Ischemic time (h)	0.068	0.022	9.245	.002	1.070	1.024-1.118
Length of stay (d)	−0.001	0.001	0.372	.542	0.999	0.997-1.001

HR, Hazard ratio; EF, ejection fraction; BMI, body mass index; UNOS, United Network for Organ Sharing. *HR compared with group 1 (EF >60%). †HR reflects the effect of a 1-year change in age. ‡HR compared with white ethnicity. §HR compared with UNOS region 6. ||HR compared with era 2012-2016. ¶HR reflects 1-unit increase in the conditional probability of donor ejection fraction group given individual covariates.

not clinically significant because all LVEF groups had normalized (Table 2).

Distribution of transplants across donor heart function groups varied significantly among UNOS regions (Table 3); however, no trend emerged between regional volume and willingness to transplant hearts with LV dysfunction. In multivariate analysis, UNOS region did emerge as an independent predictor of mortality (Tables 4 and 5), with UNOS region 6 demonstrating best overall survival.

Likewise, transplant era emerged as an independent predictor of survival (Tables 4 and 5), with the most recent era (2012-2016) having the best overall survival.

Cox regression analysis using EF as a categorical variable (Table 4) and as a continuous variable (Table 5) showed that after adjustment for propensity variation, transplant year, and transplant region, EF had no statistically significant impact on mortality.

TABLE 5. Cox regression hazard ratios and confidence intervals using left ventricular ejection fraction as a continuous variable

Parameter	Parameter estimate	Standard error	Chi-square	P value	HR	95% Wald confidence limits
Ejection fraction	−0.001	0.003	0.171	.679	0.999*	0.993-1.005
Age recipient	0.015	0.002	64.48	<.001	1.015‡	1.011-1.019
Age donor	0.003	0.002	2.491	.123	1.003‡	0.999-1.007
Female gender	0.027	0.053	0.250	.620	1.027	0.925-1.140
Race/ethnicity recipient						
Black	0.096	0.055	2.996	.084	1.101‡	0.987-1.227
Hispanic	0.013	0.095	0.019	.886	1.013‡	0.841-1.220
Asian	0.335	0.186	3.256	.075	1.399‡	0.971-2.013
American Indian	−0.067	0.417	0.026	.875	0.935‡	0.413-2.117
Native Hawaiian	−0.428	0.344	1.543	.214	0.652‡	0.332-1.280
Multiracial	0.021	0.295	0.005	.946	1.021‡	0.573-1.818
Race/ethnicity donor						
Black	0.060	0.067	0.821	.370	1.063‡	0.932-1.212
Hispanic	0.097	0.072	1.763	.180	1.101‡	0.955-1.268
Asian	0.364	0.213	2.963	.088	1.443‡	0.950-2.192
American Indian	−0.440	0.308	2.105	.153	0.640‡	0.350-1.170
Native Hawaiian	−0.343	0.715	0.219	.632	0.716‡	0.176-2.908
Multiracial	0.165	0.325	0.254	.613	1.178‡	0.623-2.229
BMI recipient	0.009	0.005	3.375	.067	1.009	0.999-1.018
Days on wait list	0.000	0.000	0.045	.834	1.000	1.000-1.000
UNOS region						
1	0.755	0.243	9.761	.002	2.135§	1.327-3.437
2	0.623	0.204	9.412	.002	1.873§	1.254-2.796
3	0.552	0.197	7.946	.005	1.745§	1.185-2.569
4	0.426	0.187	5.281	.023	1.536§	1.065-2.215
5	0.033	0.174	0.048	.847	1.039§	1.739-1.461
7	0.558	0.203	7.983	.005	1.772§	1.192-2.636
8	0.506	0.196	6.737	.010	1.664§	1.133-2.445
9	0.677	0.220	9.585	.002	1.976§	1.284-3.041
10	0.778	0.220	12.54	<.001	2.182§	1.417-3.360
11	1.095	0.225	23.81	<.001	2.998§	1.929-4.660
Era						
2000-2003	0.16909	0.03706	20.814	<.001	1.184	1.101-1.273
2004-2007	0.13619	0.03705	13.508	.0002	1.146	1.066-1.232
2008-2011	0.03944	0.03818	1.0668	.3017	1.040	0.965-1.121
Propensity score	0.153	0.034	19.85	<.001	1.166¶	1.090-1.248
Ischemic time (h)	0.068	0.022	9.245	.002	1.070	1.025-1.118
Length of stay (d)	−0.001	0.001	0.373	.541	0.999	0.997-1.001

HR, Hazard ratio; BMI, body mass index; UNOS, United Network for Organ Sharing. *HR reflects a 1% change in ejection fraction. †HR for age reflect the effect of a 1-year change in age. ‡HR compared with white ethnicity. §HR compared with UNOS region 6. ||HR compared with era 2012-2016. ¶HR reflects 1-unit increase in the conditional probability of donor ejection fraction group given individual covariates.

DISCUSSION

Our study provides modern, robust, long-term data on survival of recipients of donor hearts with suboptimal LV systolic function and suggests a pathway to explore expansion of the donor pool by reclaiming a portion of the donor pool unused because of poor function. Limitations of our work include those inherent in all retrospective, observational studies and in those dependent on manual data entry. In addition, during the period of study,

digitization of echocardiograms became more common, and therefore there was increased ability for transplant centers to review copies of the echocardiogram performed and interpreted at the procurement center. Therefore, there may have been disparities between the EF recorded at the procurement center and the transplant center's cardiologist's or surgeon's interpretation of the same echocardiogram. Furthermore, because only 1 EF is recorded in the UNOS database, it is also possible

VIDEO 1. Dr David G. Rabkin and the recipient of a donor heart with low LVEF discuss the patient's experiences. Video available at: [https://www.jtcvs.org/article/S0022-5223\(18\)32826-5/fulltext](https://www.jtcvs.org/article/S0022-5223(18)32826-5/fulltext).

that subsequent echocardiograms were performed demonstrating a change in function but not recorded in the UNOS database.

Despite these drawbacks, several useful conclusions emerge. Using a large, contemporary database and a balancing methodology that accounts for baseline differences in donor and recipient characteristics, and looking at EF as both a categorical variable guided by spline analysis and a continuous variable, we showed that after adjustment for transplant year and transplant region, EF had no statistically significant impact on mortality. At the very least, this should provide reassurance about using donor hearts with LVEF 50% to 54.9% and hopefully discourage the surprisingly common practice of nonuse of these hearts based exclusively on the perception that their function is compromised.⁶

Perhaps more compelling than the survival data was the demonstration that ventricular function across all donor heart groups normalized at approximately 1 year (Table 2 and Video 1). This supports prior experimental studies demonstrating functional recovery of hearts damaged by the pathophysiology of brain death after the organ is removed or protected from the hostile environment produced by brain death^{10,11} and suggests that studies of LV function in the setting of brain death should be interpreted cautiously.

Our study demonstrates that reduced LV systolic function alone should not be used as a basis for nonuse. This is a common occurrence. Our group has demonstrated that isolated LV systolic dysfunction is used as the sole explanation for nonuse in 19% of potential donors whose hearts were declined for transplantation, amounting to approximately 1300 hearts per year.⁶ Of the donor hearts with recorded LVEF included in that study, 60.41% had LVEF 40% or greater, included in group 2 or 3. This represents approximately 785 hearts per year.

After our article had been accepted for presentation, Dr Chen and colleagues²⁰ published a study with somewhat different methodology but demonstrating similar results.

They categorized patients into 3 cohorts by donor EF: less than 40% (reduced EF), 40% to 50% (borderline EF), and 50% or more (normal EF). Propensity score matching was performed using 1-to-1 matching without replacement to separately compare reduced EF cases with normal EF cases, and borderline EF cases with normal EF cases. Baseline variables with statistically significant differences among the cohorts were chosen for propensity score matching. Using the UNOS database, Chen and colleagues²⁰ showed that after matching baseline donor and recipient characteristics, patients who received hearts with “reduced” and “borderline” function had equivalent 1-year survival compared with patients who received hearts with LVEF greater than 50%. Our study supports and extends their results to demonstrate equivalent long-term survival of donor hearts with diminished ventricular function.

CONCLUSIONS

Alternative therapies for patients on the heart transplant waiting list include continued waiting for primary transplant with modern waiting list mortality (or removal from transplant list because of deterioration) for status 1a of 15% at 180 days,²¹ bridge to transplant using an LV assist device with equivalent short-term survival but higher incidence of pretransplant complications (gastrointestinal bleeding, pump thrombosis/failure, LV assist device-related infection, cerebrovascular accident, and development of human leukocyte antigen antibodies) with unclear impact on long-term outcomes and no guarantee of receiving a heart with normal LV function,²²⁻²⁵ high-risk conventional surgery for selected patients,²⁶ or forgoing these therapies in favor of end-of-life care.²⁷ Although even if a large number of donor hearts with reduced ventricular function were used, there would still be a significant disparity between available and needed organs. Given these alternatives, nonuse of donor hearts with diminished LVEF on the basis of depressed function alone may represent a waste of valuable organs for transplantation.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: heart transplantation, heart donor evaluation, ventricular function

Discussion

Dr Augustin Sibona (Loma Linda, Calif). [Note—the manuscript has changed substantially in the revision process since this discussion took place.]

This recent project is performed by the Department of Cardiothoracic Surgery and Radiology at Loma Linda University Medical Center with the collaboration of the Department of Medicine at Stanford University Medical Center. We have nothing to disclose. End-stage heart failure events occur in people every year, and cardiac transplantation remains the gold standard of care; however, as you see in this graphic, transplant rates have remained static over the past 15 years at 2000 to 2500 per year in the United States. Previous work from our research group has documented that 19% of the patient donor hearts are not used for transplantation entirely based on left ventricular dysfunction. This pie graph represents the total donor heart pool. Thirty-five percent of the donor hearts are being transplanted; in red, you can appreciate the proportion of hearts not being transplanted entirely based on a low EF, which is 1300 hearts a year. The goals of our project are to provide robust and long-term outcome data of adult hearts with diminished left ventricular function and determine whether expansion of the donor pool is appropriate. Data were obtained from the UNOS database. All isolated adult heart transplants in the United States between January 1, 2000, and March 31, 2016, were included. For the purposes of our study, the definition of a normal EF is more than 55%, and for exclusion criteria we have hearts transplanted along with other organs, hearts with an EF less than 20% in the pediatric population.

The donor hearts were divided into 5 groups: (1) included hearts with an EF greater than 55%; (2) hearts with EF between 50% and 54.9%; (3) EF between 40% and 49.9%; (4) EF between 30% and 39.9%; and (5) EF between 20% and 29.9%. Baseline characteristics, post-operative length of stay, and Kaplan-Meier survival curves were compared. This is a brief summary of the analysis. During the study period, 31,979 hearts were transplanted,

and we excluded 279 hearts for not having EF recorded and 788 hearts for having EF of less than 20%, so we included 30,942 hearts. Of these, 28,044 were included in group 1, 2187 were included in group 2, 595 were included in group 3, 95 hearts were included in group 4, and 21 hearts were included in group 5. The median follow-up was 1513 days. Mean age varied inversely with left ventricular function and differences were statistically significant. Group 1 had the highest proportion of female donors, and group 4 had the lowest. The mean left ventricular EF was 63%, 50%, 44%, 34%, and 23% for groups 1 through 5, respectively, and there were no statistically significant differences in cause of death, donor race, or cold ischemic times among the study groups comparisons of differences in baseline recipient characteristics. These are the Kaplan–Meier survival curves for each of the 5 groups, with survivor probability on the Y-axis and post-transplant survival in days on the X-axis. There were no statistically significant differences between the groups. The differences in the mean postoperative length of stay were statistically significant with length of stay increasing with decreasing ventricular function except for group %, which had the lowest length of stay likely due to high perioperative mortality. Cox regression analysis demonstrated that left ventricular EF is a significant predictor of mortality after adjustment for donor and recipient age. Using group 1 as a reference, recipients of hearts from group 3 and group 5 were found to have significantly higher mortality. However, group 2 is a large cohort study with survival indistinguishable from group 1. Group 3 showed equivalent postoperative length of stay and equivalent survival on univariate analysis, but diminished survival on multivariate analysis, which suggested that good results were achieved through a careful selection of the hearts. Group 4 showed equivalent survival on both univariate and multivariate analyses, although with increased postoperative length of stay. Group 5 is a small cohort with high perioperative mortality and a trend toward reduced survival after 3000 days on univariate analysis. There was an inverse relationship between donor age and left ventricular function and multivariate analysis suggests that transplant teams were more inclined to take donor hearts with poor function from young male healthy donors.

We conclude by saying that diminished left ventricular systolic function alone should not be used as a basis for nonutilization. As mentioned, 1300 hearts a year are not being used based exclusively on diminished left ventricular function; 64% of these hearts had an EF of more than 40%. This represents 785 hearts a year. If only half of these were used, it would represent an increase in the domestic transplant rate of almost 20%.

Moderator. The discussion will be opened by Murray Kwon.

Dr Murray Kwon (*Los Angeles, Calif*). Your analysis on equivalency and survival among your 5 groups is based on the Kaplan–Meier survival curve, _____ yet as you just demonstrated, when you looked at multivariate analysis _____ in your group 3 patients, those with EF of 40% to 49% actually had a higher mortality than your normal donors. The survival results you show are predicated on a younger patient population being taken, so what you've actually shown very nicely in your _____ analysis is the risk aversion of the various programs when they take these _____. So, when you cite that 19% or 1300 hearts are excluded based on dysfunction alone, are you aware of any of the rejected organs from the group of younger donors that you might have actually considered and would actually lead this strategy of accepting compromised donors would actually increase the donor pool in _____?

Dr Sibona. Yes, again in the univariate analysis, there are almost no differences in the first 4 groups. The exception is again, group 5, and in the multivariate analysis, we had a higher mortality group. This again represents and reassures what we demonstrate here, that there was probably a selection bias from the surgeons when they were going to procure hearts from younger men; they were probably more prone and more likely to retrieve and procure a heart from a young healthy man, even if the heart had a low EF. So, we're not saying that we should use each heart with an EF of 35% or 45%, but we said that you should thoroughly evaluate those patients with those hearts and consider them likely for transplantation.

Dr Kwon. Why were there longer hospital stays in group 3, again the _____ 49% group, that's really what we're targeting in terms of numbers to increase our annual transplantation. Could it be this group experienced higher degrees of primary graft dysfunction, and thus, _____ and so with what we get from the database is important to distinguish what these increased lengths of stay mean. Because death is a broad _____ indicator, and there are other things in life and death that we need to consider.

Dr Sibona. Yes, unfortunately, we don't know why this group had a higher _____ from the database that we use. We only have numbers, and we only have _____, so everything we can propose now is probably some speculation. Yes, we can propose _____ lower EF had an increased length of stay because they had increased _____ days, so probably they had an increased requirement for pressors or maybe just the surgeons who were transplanting these hearts, and they knew the EF was not optimal they were more reluctant to discharge the patient from the hospital. But again, yes, we only have the numbers from the database _____.

Dr Kwon. I'm going to shift gears a little bit. Heart transplantation and mechanical circulatory support _____ but during the first _____ of your study, _____ represented 20% of all transplants _____. That number doubled to 38% in the latter half of your trial analysis, so our makeup of patients has changed from the very sick patients _____ to relatively stable patients on LVAD support at home, _____ much better-tolerated devices as well. So would you take a compromised donor heart? Or a lower EF heart in this new environment of _____?

Dr Sibona. Yes, so _____ device, we know this evolving technology, we do have some short-term options on _____, and there are actually _____ the ventricular assistive devices are not free of complications. We know that a percent of them are going to have some sort of complication with gastrointestinal bleed, stroke, thrombosis, infections, and so we do still believe that transplants...heart transplantation _____ treatment. The question _____ heart is yes, we should remember that these patients are on end-stage heart failure. They probably cannot get out of bed, even _____ short of breath, they are probably on pressors in the hospital _____ so yes, _____.

Dr Kwon. I'd like to comment that when considering whether I or anyone should heed the recommendations or not, 91% of programs do less than 30 transplants a year and _____ 76% do less than 20. The smaller programs won't necessarily have the luxury of 3000 days to see their survival _____ they have 2 or 3 deaths a year, that's _____. So, I would urge some caution in that regard, but I want to congratulate you and your co-authors for a thoughtful study.

Moderator. Craig.

Dr Craig Selzman (*Salt Lake City, Utah*). There's probably not a more unsatisfying thing to do but to take a stable ambulatory patient and perform a transplant and end up back on an unstable _____ more common than... Are you using any EF or just the last EF before transplant?

Dr Sibona. Yes, it's the last EF before transplant. Unfortunately, again the database doesn't provide when the EF was recorded. We do know that when a patient is _____ heart, the organism is a hostile environment and probably the heart, it doesn't work as good as it used to work before, but yes, it's the last EF for the patient, but unfortunately, we don't know exactly when the echocardiogram was done.

Dr Selzman. Yeah, it seems like that's important because to your point, brain death _____ roll around and there are certain things that might get better. My follow-up question to that is although you didn't show that the mode of death was different between the groups, did you examine the group that survived and the mode of death. In other words, a patient with multisystem trauma chest versus a cerebral bleed. There's different ways you might assess that patient. Did you look into the individual group survivors and non-survivors as to mode of death?

Dr Sibona. We didn't, and it's a good idea for a follow-up study, which did have _____ database, and it has many variables, so we can have obviously that information, but we didn't _____ specifically on each group and differentiate between survivors _____.

Dr Selzman. That might be interesting when you're getting these phone calls at 2:00 AM to _____.

Moderator. Richard, quick question.

Dr Richard Shemin (*Los Angeles, Calif*). I'm interested again in the bias of the surgeon in accepting these compromised hearts. In addition to taking young male hearts with low EFs, what about the time of transport in total ischemic time? What was the ultimate EF of these hearts when the patients

left the hospital?

Dr Sibona. We do have the information for _____ no differences between the groups at all, and we do not have the EF for _____.

Dr Shemin. So, you don't know if the heart has recovered to a near normal EF?

Dr Sibona. No, we mainly focused on the mortality.