Clinical Investigation

Effects of Older Donor Age and Cold Ischemic Time

on Long-Term Outcomes of Heart Transplantation

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Using older donor hearts in cardiac transplantation may lead to inferior outcomes: older donors have more comorbidities that reduce graft quality, including coronary artery disease, hypertension, diabetes mellitus, and dyslipidemia. Shorter cold ischemic times might overcome the detrimental effect of older donor age. We examined the relationship between donor allograft age and cold ischemic time on the long-term outcomes of heart transplant recipients.

From 1994 through 2010, surgeons at our hospital performed 745 heart transplantations. We retrospectively classified these cases by donor ages of <50 years (younger) and ≥50 years (older), then by cold ischemic times of <120 min (short), 120 to 240 min (intermediate), and >240 min (long). Endpoints included recipient and graft survival, and freedom from cardiac allograft vasculopathy, nonfatal major adverse cardiac events, and rejection.

For intermediate ischemic times, the 5-year recipient survival rate was lower when donors were older (70% vs 82.6%; P=0.02). This was also true for long ischemic times (69.8% vs 87.6%; P=0.09). For short ischemic times, we found no difference in 5-year recipient or graft survival rates (80% older vs 85.6% younger; P=0.79), in freedom from nonfatal major adverse cardiac events (83.3% vs 91.5%; P=0.46), or in freedom from cardiac allograft vasculopathy (50% vs 70.6%; P=0.66). Rejection rates were mostly similar.

Long-term graft survival in heart transplantation patients with older donor allografts may improve when cold ischemic times are shorter. ***(Tex Heart Inst J 2018;45(1):17-22)***

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In the United States, the prevalence of heart failure in adults is projected to rise from 5.7 million currently to more than 8 million by 2030.[1] Survival rates after a diagnosis of heart failure have improved; however, the one-year mortality rate (~30%)[2-4] and the median survival duration (5 yr)[3] have not. In contrast, after heart transplantation, the one-year survival rate is 82% and the median survival duration is 11 years.[5] Heart transplantation improves quality of life[6] and is the sole definitive treatment for advanced heart failure. However, the finite availability and varying quality of donor organs have limited the number of transplantations performed and have adversely affected after-transplantation outcomes. Criteria that influence donor–recipient matching include physical distance and the concomitant cold ischemic time (CIT), as well as donor age, antibody profiles, body size, ABO blood type, comorbidities, and heart function.[7]

In the U.S., only 34% of potential donor hearts were accepted from 1995 through 2010, and despite national efforts to increase organ usage, donor-heart acceptance rates steadily decreased from 1995 through 2008 and increased only at the end of the analysis period (2008–2010).[8] The decline in organ usage might indicate a greater avoidance of high-risk donors. Although most high-risk factors are robustly associated with nonuse of donor organs, these factors are not reliable predictors of adverse events after transplantation.[9] Expanding the donor pool potentially involves re-evaluating the use of organs that might previously have been avoided, such as those from older donors.

The use of cardiac allografts from older donors increased over time through 2010 and then remained stable.[5] In the 2015 report from the International Society for Heart and Lung Transplantation (ISHLT), the median heart-donor age was 35 years (5th to 95th percentile, 17–57 yr).[5] Earlier ISHLT registry data revealed that older donor age was a significant predictor of death at one year and 5 years after heart transplantation, but not at 15 years; and the correlation between older donor age and higher recipient mortality rates remained significant after multivariate analysis.[10] Older donor

age has also been associated with a higher incidence of cardiac allograft vasculopathy (CAV).[11,12] Study results have indicated a possibly important interaction between CIT and donor age: CITs <3.5 hr were associated with superior survival rates, and hearts from younger donors better tolerated longer CITs.[13] Approaches to improve outcomes in recipients of older allografts are poorly defined and perhaps could include more specific criteria in regard to projected CITs. We therefore investigated the effect of CIT on transplantation outcomes when cardiac donors are older.

Patients and Methods

This study was reviewed and approved by the Cedars-Sinai Institutional Review Board.

From 1994 through 2010, 745 heart transplantations were performed in our institution. We divided this group into recipients of hearts from donors who were <50 years old and ≥50 years old, and we further categorized CIT as short (<120 min), intermediate (120–240 min), and long (>240 min) (Fig. 1). We chose the age threshold because survival rates are reportedly inferior when donor allografts are >50 years old.[14] Short CITs were associated with local donors (short travel times) and fewer repeat transplantations among patients in this subgroup. Donor selection criteria between groups varied only in terms of our institutional practice of requesting coronary angiography routinely in older donors and selectively otherwise. Younger donors underwent angiography only if additional risk factors were present, such as chronic diabetes mellitus, tobacco smoking, or family history of heart disease. In addition, we have a lower threshold for intraoperative evaluation of cardiac filling pressures when donors are older.

Endpoints. We prospectively gathered data on relevant clinical endpoints and entered them into our institution's heart transplantation research database. We retrospectively evaluated the following endpoints at 5 years after transplantation: actuarial graft survival; freedom from CAV (defined as coronary artery stenosis ≥30%); and freedom from nonfatal major adverse cardiac events (NF-MACE), defined as myocardial infarction, congestive heart failure, percutaneous coronary intervention, pacemaker or defibrillator implantation, or stroke. In addition, we evaluated one-year freedoms from treated rejection: cellular, antibody-mediated, biopsy-negative, and combined.

Statistical Analysis

We used unpaired Student *t* tests to compare continuous variables between groups (reported as mean ± SD). We used the Fisher exact test to compare categorical variables between groups (reported as percentage). Analyses of survival and freedom from events were performed by using the Kaplan-Meier method; comparison between groups was with log-rank tests. Two-tailed *P* values <0.05 were considered significant. All statistical analyses were performed with use of SPSS version 22 (SPSS Inc., an IBM company).

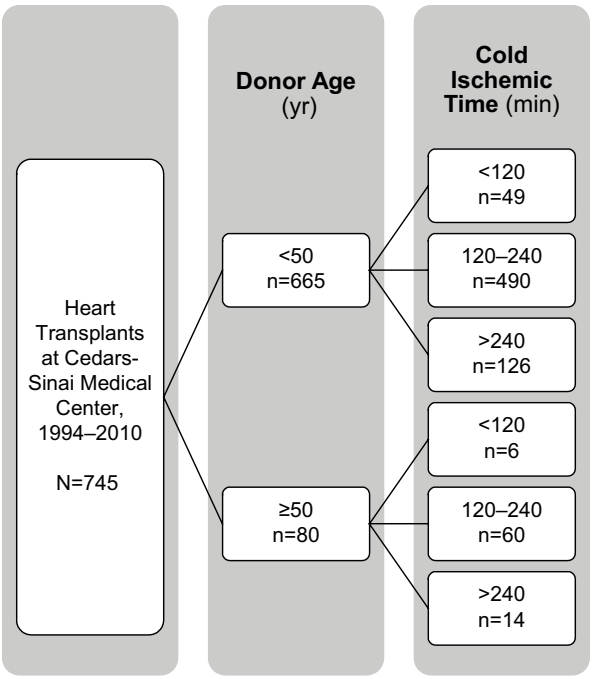

Fig. 1 *Diagram shows division of heart transplantations into 6 groups for comparison by allograft age (young, <50 yr; and old, ≥50 yr) and by cold ischemic time (short, <120 min; intermediate, 120–240 min; and long, >240 min).*

Results

Table I shows the recipients' demographic data. The mean donor age in the short-CIT group was 29.6 ± 10.9 years for those <50 versus 55.5 ± 7.4 for those ≥50 years old; for intermediate CITs, it was 29 ± 10.3 versus 53.8 ± 3.2 years; and for long CITs, it was 30.1 ± 10.1 versus 54.9 ± 2.8 years (all P <0.001). The frequency of sensitization (pretransplantation panel-reactive antibody, >10%) was higher in recipients of older hearts in the long-CIT group. In the long-CIT groups only, the prevalence of Status 1 listings was higher in the younger donor group. Other demographic variables were similar.

Our most important finding is that older donor age was not detrimental to recipient survival outcomes when CITs were short (Fig. 2). No recipient in the short-CIT group needed mechanical circulatory support after transplantation. For intermediate CITs, the 5-year recipient survival rate was significantly lower when donors were older (70% vs 82.6%; P=0.02) (Table II). Similar results were seen for long CITs: 69.8% for older donors versus 87.6% for younger (P=0.09). In contrast, for short CITs, we found no significant difference in 5-year survival rates in terms of age (80% vs 85.6%; P=0.789).

TABLE I. Characteristics of the 745 Heart Transplantations

Variable	Cold Ischemic Time								
	<120 min			120–240 min			>240 min		
	<50 yr (n=49)	≥50 yr (n=6)	*P* Value	<50 yr (n=490)	≥50 yr (n=60)	*P* Value	<50 yr (n=126)	≥50 yr (n=14)	*P* Value
Recipient age (yr)	56.6 ± 8.6	55.2 ± 8.4	0.708	58.2 ± 7.4	58.3 ± 8.1	0.922	58 ± 7.6	61.3 ± 8.3	0.129
Donor age (yr)	29.6 ± 10.9	55.5 ± 7.4	<0.001	29 ± 10.3	53.8 ± 3.2	<0.001	30.1 ± 10.1	54.9 ± 2.8	<0.001
Body mass index	25.8 ± 4.5	24.7 ± 7.6	0.604	25.2 ± 4.5	25.5 ± 4.6	0.627	25.1 ± 4.2	24.4 ± 2.7	0.544
Female	13 (26.5)	1 (16.7)	0.999	122 (24.9)	19 (31.7)	0.275	21 (16.7)	2 (14.3)	0.999
Previous pregnancy	10 (76.9)	1 (100)	0.476	97 (79.5)	15 (78.9)	0.999	15 (71.4)	2 (100)	0.57
Prior blood transfusion	1 (2)	0	0.999	77 (15.7)	14 (23.3)	0.142	37 (29.4)	4 (28.6)	0.999
Pretransplant PRA ≥10%	4 (8.2)	0	0.999	51 (10.4)	8 (13.3)	0.506	19 (15.1)	5 (35.7)	0.066
Ischemic time (min)	102.4 ± 14.9	91 ± 22.4	0.1	176.9 ± 32.6	181 ± 32.3	0.358	283.7 ± 44.9	290.4 ± 46.5	0.598
Recipient CAD	26 (53.1)	2 (33.3)	0.422	262 (53.5)	33 (55)	0.891	69 (54.8)	9 (64.3)	0.579
Status 1 at transplant	29 (59.2)	3 (50)	0.686	257 (52.4)	25 (41.7)	0.133	67 (53.1)	4 (28.6)	0.097
CMV mismatch	13 (26.5)	2 (33.3)	0.696	92 (18.8)	11 (18.3)	0.999	26 (20.6)	3 (21.4)	0.999
Diabetes mellitus	8 (16.3)	3 (50)	0.087	128 (26.1)	12 (20)	0.349	42 (33.3)	6 (42.9)	0.556
Treated hypertension	13 (26.5)	3 (50)	0.096	186 (38)	26 (43.3)	0.483	56 (44.4)	7 (50)	0.78
MCS device	3 (6.1)	0	0.999	55 (11.2)	6 (10)	0.999	31 (24.6)	3 (21.4)	0.999

CAD = coronary artery disease; CMV = cytomegalovirus; MCS = mechanical circulatory support; PRA = panel-reactive antibody

Data are presented as mean ± SD or as number and percentage. $P<0.05$ was considered statistically significant.

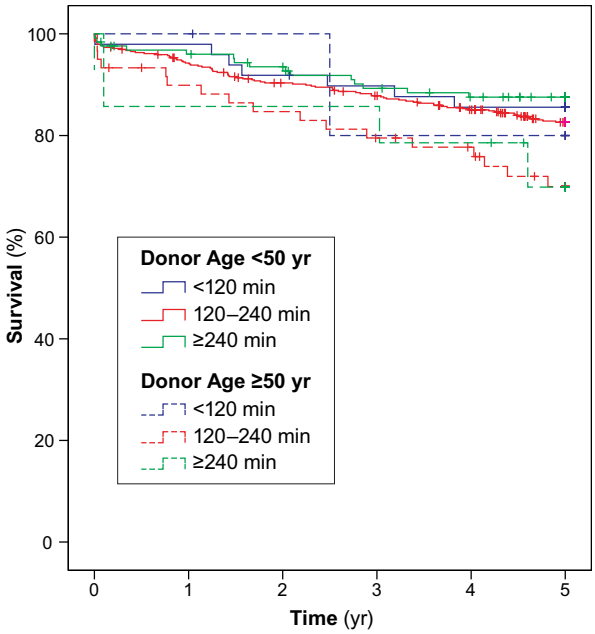

Fig. 2 *Graph shows Kaplan-Meier estimates of 5-year actuarial patient survival after heart transplantation, grouped by allograft age and cold ischemic time. At short ischemic times, recipients of older and younger hearts had similar 5-year survival rates. Tick marks denote censoring.*

In older-allograft recipients in the long-CIT subgroups, we identified no differences in graft survival (69.8% older vs 86% younger; $P=0.151$), freedom from CAV (69.4% vs 80.7%; $P=0.62$), or freedom from NF-MACE (76.2% vs 88.9; $P=0.134$). For intermediate CITs, these 3 outcomes were significantly poorer in recipients of older allografts ($P=0.008$, $P=0.001$, and $P=0.034$). For short CITs, we found similarity in 5-year graft survival rates (80% vs 85.6%; $P=0.789$), freedom from CAV (50% vs 70.6%; $P=0.663$), and freedom from NF-MACE (83.3% vs 91.5%; $P=0.464$).

Older donor allografts were associated with less freedom from treated cellular rejection than were younger ones for short CITs (66.7% vs 95.8%; $P=0.004$), but not for intermediate or long CITs. We identified no significant differences in other rejection rates.

The causes of death in recipients were similar across the groups (Table III). Chief among these were noncytomegalovirus infection, graft failure, rejection, and CAV.

Discussion

Older donor age and long CIT have consistently correlated with higher one-year mortality rates after heart transplantation.[5,10,15-17] Less established is whether mini-

TABLE II. Outcomes by Cold Ischemic Time and Donor Age

Endpoints	Cold Ischemic Time								
	<120 min			120–240 min			>240 min		
	<50 yr (n=49)	≥50 yr (n=6)	*P* Value	<50 yr (n=490)	≥50 yr (n=60)	*P* Value	<50 yr (n=126)	≥50 yr (n=14)	*P* Value
5-Year actuarial									
Recipient survival	85.6	80	0.789	82.6	70	0.02	87.6	69.8	0.09
Graft survival	85.6	80	0.789	82.4	68.35	0.008	86	69.8	0.151
Freedom from CAV	70.6	50	0.663	76	51.1	0.001	80.7	69.4	0.62
Freedom from NF-MACE	91.5	83.3	0.464	80.8	68.5	0.034	88.9	76.2	0.134
1-Year freedom									
Any treated rejection	85.5	66.7	0.254	88.3	89.4	0.808	86.1	76.2	0.353
Treated cellular rejection	95.8	66.7	0.004	94.8	94.7	0.958	94.2	83.9	0.158
Treated antibody-mediated rejection	91.7	100	0.473	94.2	94.7	0.839	92.7	92.3	0.944
Biopsy-negative rejection	97.9	100	0.724	98.3	98.2	0.948	97.5	100	0.579

CAV = cardiac allograft vasculopathy defined by ≥30% coronary artery stenosis; NF-MACE = nonfatal major adverse cardiac events (myocardial infarction, congestive heart failure, percutaneous coronary intervention, pacemaker or defibrillation implantation, or stroke)

Data were calculated with use of the Kaplan-Meier method and are presented as percentage. $P < 0.05$ was considered statistically significant.

TABLE III. Causes of Death in Allograft Recipients by Cold Ischemic Time and Donor Age

Cause of Death	Cold Ischemic Time						Overall
	<120 min		120–240 min		>240 min		
	<50 yr (n=49)	≥50 yr (n=6)	<50 yr (n=490)	≥50 yr (n=60)	<50 yr (n=126)	≥50 yr (n=14)	
CAV	0	0	13 (2.7)	1 (1.7)	0	1 (7.1)	15 (2)
Rejection	0	0	11 (2.2)	4 (6.7)	4 (3.2)	0	19 (2.6)
Lymphoma	0	0	0	0	1 (0.8)	0	1 (0.1)
Other malignancy	0	0	8 (1.6)	0	0	0	8 (1.1)
Non-CMV infection	1 (2)	0	15 (3.1)	5 (8.3)	5 (4)	1 (7.1)	27 (3.6)
Graft failure	5 (10)	1 (16.7)	12 (2.4)	2 (3.3)	2 (1.6)	2 (14.3)	24 (3.2)
Technical failure	0	0	1 (0.2)	0	2 (1.6)	0	3 (0.4)
Other	0	0	4 (0.8)	1 (1.7)	1 (0.8)	0	6 (0.8)
Renal failure	0	0	2 (0.4)	0	0	0	2 (0.3)
Pulmonary	1 (2)	0	4 (0.8)	3 (5)	0	0	8 (1.1)
Cerebrovascular	0	0	5 (1)	1 (1.7)	0	0	6 (0.8)
Unknown	0	0	8 (1.6)	0	0	0	8 (1.1)
TOTAL	7 (14.3)	1 (1.7)	83 (16.9)	17 (28.3)	15 (11.9)	4 (28.6)	127 (100)

CAV = cardiac allograft vasculopathy (≥30% coronary artery stenosis); CMV = cytomegalovirus

No patient died of multiple-organ failure. Data are presented as number and percentage.

mizing CIT reduces the negative influence of older age. In the current study, 5-year survival rates at short CITs were similar regardless of allograft age; however, at CITs beyond 120 min, the negative impact of older age was apparent.

Damage to harvested organs can occur after periods of relative hypoxia and limited nutrient availability, followed by additional injury and inflammation associated with reperfusion. Because of age-associated changes, an older donor heart may be particularly susceptible to injury and have less regenerative capacity.[18] Left ventricular hypertrophy may also have negative effects. Therefore, optimal organ preservation and short CIT would seem to be particularly important in older cardiac allografts. An important consideration for future research is whether older donor hearts can benefit from alternative protective approaches, such as improved perfusion during transportation.

Investigators have reported an association between donor age and CIT, with a negative impact of CIT on recipients' survival outcome that was significant only when donors were older than 50 years.[14] Authors who analyzed the United Network for Organ Sharing database for recipient survival rates after heart transplantation reported a significant effect of CIT that depended on donor age, with greater tolerance for prolonged CITs when grafts came from younger donors.[13] The results of the current study confirm an important relationship between donor age, CIT, and outcomes, and implies that older hearts are more viable at CIT <120 min.

We are typically cautious about accepting older hearts with long CITs. However, if a recipient's status is deteriorating, we might accept greater risk if all other donor variables are favorable, such as short harvest time, the absence of coronary artery disease and left ventricular hypertrophy, and death from causes other than cerebrovascular accident.

Limitations. Our study is subject to the limitations inherent to a retrospective analysis, including the potential for selection bias and other confounding variables. In addition, this study was observational and uncontrolled; however, substantial logistic and ethical challenges would complicate a prospective, randomized study of CITs for younger and older donors. Sample sizes were small, particularly in the short- and long-CIT groups, so our findings need larger studies for confirmation.

Conclusion

We found that recipients of older hearts at short CITs (<120 min) had long-term outcomes comparable to those of recipients of younger hearts at CITs <120 min. Recipients of older hearts at a CIT of either 120 to 240 min or >240 min had worse 5-year outcomes than did recipients of younger hearts in each time group. Long-term graft survival in heart transplantation patients with older donor allografts may improve when CITs are shorter.

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