The Journal of Heart and Lung Transplantation. 2015; 34(6): 790-796

Heart transplantation using allografts from older donors: multicenter study results

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Abstract.
BACKGROUND. The lengthy waiting time for heart transplantation is associated with high mortality. To increase the number of donors, new strategies have emerged, including the use of hearts from donors ≥50 years old. However, this practice remains controversial. The aim of this study was to evaluate outcomes of patients receiving heart transplants from older donors.
METHODS. We retrospectively analyzed 2,102 consecutive heart transplants in 8 Spanish hospitals from 1998 to 2010. Acute and overall mortality were compared in patients with grafts from donors ≥50 years old versus grafts from younger donors.
RESULTS. There were 1,758 (84%) transplanted grafts from donors < 50 years old (Group I) and 344 (16%) from donors ≥50 years old (Group II). Group I had more male donors than Group II (71% vs 57%, p = 0.0001). The incidence of cardiovascular risk factors was higher in older donors. There were no differences in acute mortality or acute rejection episodes between the 2 groups. Global mortality was higher in Group II (rate ratio, 1.40; 95% confidence interval, 1.18–1.67; p = 0.001) than in Group I. After adjusting for donor cause of death, donor smoking history, recipient age, induction therapy, and cyclosporine therapy, the differences lost significance. Group II had a higher incidence of coronary allograft vasculopathy at 5 years (rate ratio, 1.67; 95% confidence interval, 1.22–2.27; p = 0.001).
CONCLUSIONS. There were no differences in acute and overall mortality after adjusting for confounding factors. However, there was a midterm increased risk of coronary allograft vasculopathy with the use of older donors. Careful selection of recipients and close monitoring of coronary allograft vasculopathy are warranted in these patients.

Keywords
Heart transplantation; Older donors; Cardiac allograft vasculopathy; HTx prognosis; Survival after HTx

Heart transplantation (HTx) improves survival in selected patients with end-stage congestive heart failure.[1] In Spain, as in many countries, the availability of cardiac grafts has decreased, while the number of patients with heart failure listed for HTx remains stable or has increased.[2] Despite the increased use of a left ventricular assist device (LVAD) as a bridge to HTx to wait for a younger donor, this approach has some risks that can affect outcome after transplantation. For example, receptor sensitization and higher risk of bleeding or device infection[3] may affect survival after HTx. Also, the LVAD increases HTx cost, and some countries indicate its use only in highly selected patients. New strategies have been developed to increase the number of available grafts, including the acceptance of older donors. Although the upper donor age limit is 60 to 65 years, using donors > 50 years old raises concerns about outcomes, such as whether patients with grafts from older donors have greater susceptibility to early coronary allograft vasculopathy (CAV) and higher mortality.[4,5] The aim of this multicenter study was to investigate outcomes of patients receiving grafts from donors ≥ 50 years old.

Methods

From January 1998 to December 2010, HTx programs at 8 centers in Spain performed 2,102 consecutive HTx surgeries. Only patients > 16 years old were included in the study, and patients were divided into 2 groups according to donor age. Group I had received grafts from donors < 50 years old, and Group II had received grafts from donors ≥ 50 years old. Patients with an additional organ transplantation or heart re-transplantation were excluded from the study.

Donor information and recipients' clinical HTx data, coronary allograft vasculopathy incidence, and survival data are routinely recorded in the Spanish Register for Heart Transplantation. Pre-transplant clinical variables analyzed for recipients were age, sex, and the etiology of heart failure. Donor-related variables were age, cause of death, and history of dyslipidemia, hypertension, diabetes mellitus, and smoking. Donor diabetes mellitus type 1 or type 2 insulin-dependent was a criterion for non-acceptance. Post-HTx data analysis included ischemic time, acute rejection episodes, CAV, and overall mortality. Coronary angiography was performed to evaluate the presence of coronary disease related to the donor graft at 1 month and 1, 5, and 10 years after transplantation and when clinically indicated. Endomyocardial biopsies, echocardiography, and patient follow-up were done as needed at each center and according to its own protocol. Acute rejection was diagnosed when the pathologist graded it as AR ≥ 2R following the International Society for Heart and Lung Transplantation (ISHLT) classification. The diagnosis of CAV followed the ISHLT classification: not significant (CAV0), mild (CAV1), moderate (CAV2), and severe (CAV3)[6]; the presence of CAV1 through CAV3 was considered a CAV diagnosis. All centers used triple immunosuppressive therapy comprising steroids, cyclosporine or tacrolimus, mycophenolate mofetil or mycophenolic acid, or azathioprine or rapamycin or everolimus. Cytomegalovirus prophylaxis was given when there was a ($donor^{+}$/$receptor^{-}$) mismatch or evidence of positive CMV on polymerase chain reaction. All patients provided signed informed consent for inclusion in the HTx register and related data analysis.

Statistical analysis

Donor and recipient variables were compared between Groups I and II (donor < 50 years old and donor ≥ 50 years old, respectively). Differences between groups were analyzed by the Pearson chi-square test for qualitative variables or Mann-Whitney *U* non-parametric test for continuous variables. Acute mortality included all deaths during the admission for the HTx procedure or, among patients discharged alive after the HTx procedure, all deaths during the first month after HTx. Acute mortality was computed as a proportion with its 95% confidence interval (CI), and logistic regression was used to compute crude and adjusted odds ratios between groups. Global mortality rate and CAV incidence per 1,000 patient-years with 95% CI were calculated for each donor age group. Relative risks between groups were computed by means of a Poisson regression model with Group I always the reference group. Potential confounders both for the logistic regression (for acute mortality) and for the Poisson models (for global mortality) were selected

among variables associated with mortality and the inclusion of which individually changed > 3% the estimate (either the rate ratio [RR] or the odds ratio [OR]) from the unadjusted one.

A competing risks analysis was used to adjust CAV RRs.[7] Differences in survival between the 2 groups were examined using a Kaplan-Meier actuarial analysis and compared with a log-rank test. A p-value < 0.05 was considered significant. Data were analyzed using Stata version 12.0 (StataCorp LP, College Station, TX).

Results

Overall, 1,758 (83%) recipients received grafts from donors < 50 years old (Group I), and 344 (16%) recipients received grafts from donors ≥ 50 years old (Group II); only 18 (5%) donors were ≥ 60 years old. The number of transplants by year and donor age is shown in Table 1; the use of older donors has increased in recent years. There was no difference between age groups in the need for urgent HTx (27.9% in Group I vs 25.7% in Group II). Similarly, although there was a trend toward longer ischemic time with the use of older donors, ischemic time did not differ between groups (188 + 64 minutes vs 194 + 65 minutes, $p = 0.09$). Clinical characteristics of donors are summarized in Table 2. Group II had a higher percentage of female donors (28.6% vs 42.4%, $p = 0.0001$). Cerebral trauma as a cause of death was higher in Group I (45.7% vs 16.2%, $p = 0.0001$), but cerebrovascular accidents were more prevalent in Group II (30.1% vs 49.9%, $p = 0.0001$). Three coronary risk factors — hypertension, dyslipidemia, and smoking history — were more prevalent in Group II, but there was no difference between donor groups in diabetes mellitus incidence. Clinical characteristics of recipient groups according to donor age are shown in Table 3. Group II recipients were older (52 + 11 years old vs 55 + 10 years old, $p = 0.0001$) and had higher incidence of hypertension (29% vs 37%, $p = 0.004$) and diabetes mellitus (13.9% vs 19.5%, $p = 0.007$). Induction therapy with OKT3 was more prevalent in Group I, and induction therapy with basiliximab was more prevalent in Group II. Use of tacrolimus and mycophenolate mofetil as immunosuppressive therapy was more prevalent in Group II. Mean follow-up duration was 5.7 + 3.8 years for Group I and 5.7 + 3.7 years for Group II.

Table 1. Number of Heart Transplantations by Donor Age per Year

	Donor < 50 years old		Donor ≥ 50 years old	
Year of HTx	*n*	%	*n*	%
1998	179	89.5	21	10.5
1999	181	89.2	22	10.8
2000	181	88.3	24	11.7
2001	164	83.2	33	16.8
2002	141	84.9	25	15.1
2003	132	86.8	20	13.2
2004	125	84.5	23	15.5
2005	140	85.9	23	14.1
2006	116	82.9	24	17.1
2007	102	80.3	25	19.7
2008	117	79.1	31	20.9
2009	97	77.6	28	22.4
2010	83	64.8	45	35.2

HTx, heart transplantation.

Table 2. Donor Clinical Characteristics by Donor Age Group

	Donor < 50 years old	Donor ≥ 50 years old	
	n = 1,758	*n* = 344	*p*-value[a]
Males	71.5	57.6	< 0.001
Cause of death			
Cerebral trauma	45.7	16.2	< 0.001
CVA	30.3	49.9	
Other	25.5	34.8	
CMV serology (+)	71.6	81.9	< 0.001
Hypertension	5.6	19.7	< 0.001
Dyslipidemia	3.1	9.5	< 0.001
Diabetes mellitus ID	0.7	0.6	0.808
Smoking history			
Smoker (within 1 year)	22.6	33.1	
Ex-smoker (1–10 years)	17.7	18.8	< 0.001
Non-smoker	59.6	47.9	
Dopamine (μg/Kg/min)			
No	49.1	59.6	0.002
0–5	20.0	16.3	
> 5	30.9	24.1	
Dobutamine (μg/Kg/min)			
No	91.9	95.3	0.041
0–5	2.2	2.0	
> 5	6.0	2.6	
Noradrenaline (μg/Kg/min)			
No	55.0	50.3	0.261
0–0.05	7.6	10.2	
0.06–0.10	8.0	10.5	
0.11–0.20	9.9	11	
0.21–0.5	12.3	10.8	
> 0.5	7.2	7.3	

All results expressed as percentages. CMV, cytomegalovirus; CVA, cerebrovascular accident; ID, insulin-dependent.
[a] Pearson chi-square test.

There were no differences between Groups I and II in the number of acute rejection episodes (≥ 2R), rejection with hemodynamic compromise, or any treated rejection episode during follow-up (42.6% vs 40.1%, $p = 0.39$). Despite a ack of significant differences between the 2 groups in CAV incidence at 1 year, the incidence was significantly higher in Group II at 5-year follow-up (28.4% vs 53.0%; RR, 1.87; 95% CI, 1.37–2.55; $p = 0.0001$) and after 10 years (31.6% vs 49%; RR, 1.55; 95% CI, 1.19–2.02; $p = 0.001$), and the differences persisted after adjusting for competitive risks (Table 4).

Overall mortality was significantly higher in Group II than in Group I. Multivariate analysis showed an increased risk of death with the use of older donors (RR, 1.40; 95% CI, 1.18–1.67; $p < 0.001$). However, the significance was lost after adjusting for donor cause of death, donor smoking history, recipient age, and induction and cyclosporine therapy. Survival at 30 days was 88% (95% CI, 86.9–89.6). There were no differences between the 2 groups in crude acute mortality and after adjusting for donor cause of death, ischemic time, induction therapy, cyclosporine, tacrolimus, and mycophenolate mofetil therapies (Table 5). Survival curves showed no differences in acute mortality between Group I and Group II but increased overall crude mortality in Group II (Figure 1). When comparing the effect of donor age on survival among recipients of different age, there was a tendency for a better survival among recipients who received a heart from a donor < 50 years old, but this difference was statistically significant only in the group of recipients > 60 years old, and the effect disappeared after adjustment for confounding factors.

Table 3. Recipient Clinical Characteristics by Donor Age Group

Variable	Donor < 50 years old *n* = 1,758	Donor ≥ 50 years old *n* = 344	*p*-value[a]
Sex			
Male	80.7	79.1	0.481
Female	19.3	20.9	
Age group			
16–60 years	74.1	64.0	0.000
> 60 years	25.9	36.0	
Antecedents of hypertension			
No	71.1	63.3	0.004
Yes	29.4	36.6	
Hypercholesterolemia			
No	63.6	66.2	0.366
Yes	36.3	33.7	
Diabetes mellitus ID			
No	86.1	80.5	0.007
Yes	13.9	19.7	
Smoking history			
Smoker (within 1 year)	25.7	21.8	0.209
Ex-smoker (1–10 years)	32.0	32.5	
Non-smoker	42.2	45.6	
CMV serology			
Positive	82.4	86.0	0.159
Negative	17.4	14.0	
HTx code			
Urgent	27.9	25.7	0.416
Elective	72.1	74.4	
Induction therapy			
None	5.6	6.4	< 0.001
ALG-ATG	8.2	9.6	
OKT3	35.0	23.3	
Daclizumab	13.1	10.2	
Basiliximab	32.4	41.9	
Other	5.7	8.7	
Immunosuppressive treatment			
Cyclosporine	67.4	58.4	0.001
Tacrolimus	23.8	30.2	0.011
Azathioprine	26.3	17.4	0.000
MMF	66.8	74.1	0.008
EC-MPS	0.7	0.6	0.750
Rapamycin	2.3	0.6	0.040
Everolimus	1.9	2.6	0.370
Steroids	95.5	94.8	0.550
Variable	Mean (SD)	Mean (SD)	*p*-value[a]
Recipient age	52 ± 11	55 ± 10	0.000
Ischemic time (minutes)	188 ± 64	194 ± 65	0.095

All results expressed as percentages. ALG-ATG, anti-thymoglobulin; CMV, cytomegalovirus; EC-MPS, mycophenolic acid; HTx, heart transplantation; ID, insulin-dependent; MMF, mycophenolate mofetil; OKT-3, muromonab-CD3; SMF, mycophenolic acid.

[a] Pearson chi-square test

Table 4. Coronary Allograft Vasculopathy Incidence per 1,000 Patients/Year Comparing Recipients Transplanted with Donors < 50 Years Old or ≥ 50 Years Old

	Patient-years	CAV	Rate	95% CI	
1-year CAV incidence					
Donor < 50 years old	1,438.6	49	34.1	25.7	45.1
Donor ≥ 50 years old	262.0	13	49.6	28.8	85.5
5-year CAV incidence					
Donor < 50 years old	5,991.0	170	28.4	24.4	33.0
Donor ≥ 50 years old	980.4	52	53.0	40.4	69.6
10-year CAV incidence					
Donor < 50 years old	9,091.8	287	31.6	28.1	35.4
Donor ≥ 50 years old	1,368.7	67	49.0	38.5	62.2
	RR	95% CI		*p*-value	
Unadjusted for competitive risks					
1 year	1.46	0.79	2.68	0.228	
5 years	1.87	1.37	2.55	0.000	
10 years	1.55	1.19	2.02	0.001	
Adjusted for competitive risks					
1 year	1.39	0.75	2.56	0.296	
5 years	1.67	1.22	2.27	0.001	
10 years	1.35	1.03	1.76	0.028	

CAV, coronary allograft vasculopathy; CI, confidence interval; RR, rate ratio.

Table 5. Acute Mortality (%) and Global Mortality per 1,000 Patients/Year and Comparison of Recipients Transplanted with Donors < 50 Years Old or ≥ 50 Years Old

Global mortality	Patient-years	Deaths	Rate	95% CI	
Donor < 50 years old	11,311.1	709	62.7	58.2	67.5
Donor ≥ 50 years old	1,741.7	153	87.9	75.0	102.9
Acute mortality[a]	Patients	Deaths	%	95% CI	
Donor < 50 years old	1.758	267	15.2	13.5	17.0
Donor ≥ 50 years old	344	65	18.9	14.9	23.4
Global mortality	RR	95% CI		*p*-value	RC (%)
Unadjusted	1.40	1.18	1.67	< 0.001	
Adjusted[b]	1.19	0.96	1.47	0.111	15.27
Acute mortality	OR	95% CI		*p*-value	RC (%)
Unadjusted	1.30	0.96	1.76	0.085	
Adjusted[c]	1.17	0.81	1.70	0.407	10.08

CI, confidence interval; OR, odds ratio; RC, relative change; RR, rate ratio.
[a] Includes all deaths during the admission for the heart transplantation procedure or, among patients discharged alive after the procedure, all deaths during the first month after heart transplantation.
[b] Adjusted by donor cause of death, donor smoking history, age, induction therapy, cyclosporine, and mycophenolate mofetil.
[c] Adjusted by age, ischemic time, cyclosporine, tacrolimus, and mycophenolate mofetil.

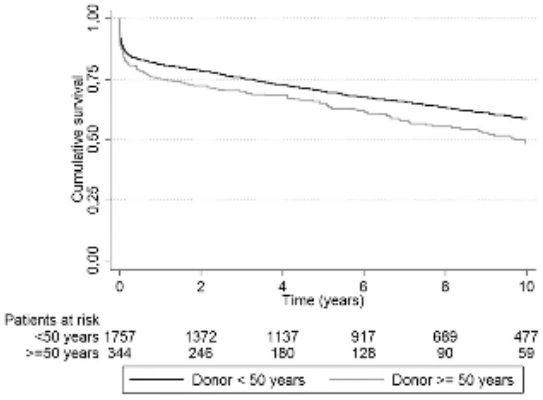

Figure 1. Differences in survival between the 2 groups using a Kaplan-Meier actuarial analysis and compared with a log-rank test. Overall crude mortality was higher with the use of older donors ($p < 0.001$)

Discussion

The present study is one of the largest to analyze the survival after HTx of patients with grafts from older donors, having prospectively recruited patients from 8 centers in Spain that send their data to the Spanish Register for Heart Transplantation. Our analysis indicates that donors ≥ 50 years old can be safely used for HTx: After adjusting for potential confounding factors, there were no differences in acute or overall mortality.

Despite the gradually increasing use of older donors, there is still controversy concerning the prognosis of recipients who receive older grafts.[8–12] Previous reports on the outcome of grafts from older donors are based on single-center studies with a small number of patients.[8,9] Although some earlier studies reported increased in-hospital mortality after accepting older donors,[13–15] we as well as others[9,16] found no differences related to donor age in acute mortality in patients undergoing HTx. Advances in acute care after HTx can explain the differences between studies performed > 10 years ago and more recent findings. In our study, the percentage of urgency codes and length of ischemic times were similar between the 2 groups, and we observed no differences in the severity of heart failure before HTx.

Overall mortality was significantly higher in Group II. However, the differences disappear after adjustment for donor cause of death, donor smoking history, recipient age, induction therapy, and cyclosporine therapy. Recipient characteristics rather than donor age can influence graft survival. Although a donor' s coronary risk factors may influence HTx outcome, this has been minimally addressed in previous studies of survival after HTx.[16,17] In our study, although the overall incidence of risk factors was low, older donors had a higher rate of hypertension, dyslipidemia, and smoking, but there were no differences in diabetes mellitus rate between donor age groups. Careful donor selection is key, and diabetes mellitus, if severe, is generally an exclusion factor for donor acceptance. In our study, the acceptance rate of a donor with diabetes mellitus was < 1%. Hypertension has been associated with diastolic dysfunction, which is not well measured at the time of HTx but can result in increased stiffness of the heart and hypertrophy. However, these factors are not associated with worse outcomes.[18] In disagreement with a previous study,[19] we did not find a significant interaction between prolonged ischemic time and the use of old donors. In the study by Russo et al, 19 patients with an ischemic time > 5.5 hours had worse survival. Because the mean ischemic time of our patients undergoing HTx was shorter, we cannot rule out that with prolonged ischemic times the use of old donors can be associated with worse prognosis. Several scores[20,21] have been proposed to evaluate donor risk and predict prognosis, suggesting that a model based on several factors would improve donor acceptance.[22]

In this study, the group of older recipients (> 60 years old) received a higher proportion of hearts from old donors rather than younger donors (< 60 years), and older recipient age has been consistently associated with worse survival in analyses of the United Network for Organ Sharing Registry.[23,24] Although induction therapy differed between the 2 study groups, this did not affect acute mortality (OKT3 was more frequently used with younger donor grafts, whereas the more recent use of older grafts coincided with increased use of basiliximab therapy). However, the influence of induction therapy on long-term prognosis is less clear.[25] Because of changes in immunosuppressive therapy in recent years, tacrolimus was more frequently given to recipients transplanted with older donor grafts. Used in combination with tacrolimus, mycophenolate mofetil and prednisone could contribute to improve survival in heart transplant recipients with older donors; this has been reported as the best immunosuppressive combination in terms of its association with less acute rejection and better survival.[26] After adjusting for confounding factors such as donor cause of death and smoking history and recipient age and immunosuppressive regimen, mortality was not increased with the use of older donors. However, the higher incidence of co-morbidities in older recipients could influence survival after HTx, especially the higher incidence of diabetes mellitus in Group II recipients. Diabetes mellitus has been associated with worse long-term outcome after HTx in previous studies.[17]

In agreement with previous data, we found no differences between the 2 groups in acute rejection or any treated rejection episodes.[10] In this study, the rejection rate was high compared with other more recent reports; differences in immunosuppressive protocols over time may explain the differences.[27] The use of older donors was associated with an increased risk of CAV at 5-year and 10-year follow-up. Although several studies[8,10] have observed no differences in CAV incidence between younger and older donors, a more recent United Network for Organ Sharing report identified older donor age as an independent risk factor for development of CAV regardless of the recipient's age.[4]

Because patients with end-stage heart failure have very high mortality while awaiting heart transplantation, implanting a LVAD to wait for what is considered a good donor is an alternative to the use of older donors.[3,28] However, LVAD use also has limitations, such as high demand on resources and higher rate of infection, hemorrhage, or thrombosis with embolic events.[3,29,30] Although the rate of complications is being reduced with the implantation of newer devices, the risk of sensitization has not decreased and is associated with increases in immunosuppressive regimens and in risk of rejection after transplantation.[31] Long-term implantation of LVADs is infrequently used in Spain, but short-term LVAD implantation is widely used when there is hemodynamic instability and urgent HTx is needed.[2] Spain's comparatively short wait-list time (< 6 months in 2012 for non-emergency HTx[32])may explain the low LVAD implantation rate. Nonetheless, long-term LVAD programs are now becoming more common because patients with pulmonary hypertension or a large body surface area may wait longer for HTx. The progressive lack of younger donors has led to a more frequent use of grafts from older donors.[2] The literature lacks studies that compare survival and cost/benefit achieved with both strategies.

A limitation of this study is that it was a retrospective study. However, the study population is considered representative because all heart transplants performed in Spain are prospectively entered in the Spanish Register for Heart Transplantation.

In conclusion, in this study, the use of selected grafts from donors ≥ 50 years old was safe. There were no differences in acute or long-term survival after adjusting for confounding factors such as recipient age or immunosuppressive regimen. However, there was a mid-term increased risk of coronary graft vasculopathy with the use of older donors. Careful selection of recipients and close monitoring of CAV are warranted in these patients.

Disclosure statement
The authors thank Elaine Lilly, Ph.D., for English language revision of the manuscript and to all Spanish National Register for Heart Transplantation participants.
This study was presented at the 33rd Annual Meeting and Scientific Session of the International Society for Heart and Lung Transplantation, April 24–27, 2013, Montreal, Canada.
This study was supported in part by the Spanish Network on Cardiovascular Research (RIC, Instituto Salud Carlos III, RD12/0042/000). None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript.

Appendix
The rest of the participants in the Spanish Heart Transplantation Registry are as follows: Vicens Brossa, MD,[a] Laura López, MD,[a] Alessandro Sionis, MD,[a] Virgilio Martinez-Mateo, MD,[a] Luis Martínez-Dolz, MD,[b] M. Jesús Paniagua-Martin, MD,[c] Raquel Marzoa-Rivas, MD,[c] Eduardo Barge-Caballero, MD,[c] Francisco Estevez-Cid, MD,[c] Luis Alonso-Pulpón, MD,[d] Manuel Gómez-Bueno, MD,[d] M. Dolores Grarcia-Cosio, MD,[d] Marta Paradinas, MD,[e] Maria Vicente, MD,[e] Nuria Ochoa, MD,[e] Miguel Angel Gómez-Sánchez, MD,[e] Montserrat Cardona, MD,[f] M. Angeles Castel, MD,[f] Marta Ferrero, MD,[f] Beatriz Diaz-Molina, MD,[g] and M Sanz-Julve, MD.[h]

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