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Lack of donor and recipient age interaction in cardiac transplantation

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BACKGROUND: The proportion of older donors and recipients is constantly rising in heart transplantation (HTX). The impact of age on different outcomes after HTX has been studied; however, effects of interaction between donor and recipient age remain elusive.

METHODS: This retrospective cohort study comprised 1,190 patients who underwent HTX between 1984 and 2011 at the Medical University Vienna. Multivariable models consisted of a basic set that included donor age, recipient age, and transplant eras and were adjusted for 2 sets of 6 possible confounders and 3 mediator variables. Cox models were used to estimate the risk of death. To search for age-related effects on the development of cardiac allograft vasculopathy (CAV), we applied cause-specific Cox models and proportional sub-distribution hazard models for competing risk data.

RESULTS: Survival was 80%, 77%, 69%, and 56% after 1, 2, 5, and 10 years, respectively. Donor age (hazard ratio [HR], 1.1; 95% confidence interval [CI], 1.0–1.2), recipient age (HR, 1.1; 95% CI, 1.0–1.2), admission from intensive care unit to HTX (HR, 1.5; 95% CI, 1.2–1.9), and diabetes (HR, 1.4; 95% CI, 1.1–1.7) were identified as significant independent risk factors for death. Significant risk factors for CAV were donor age (HR, 1.4; 95% CI, 1.3–1.5) and male recipient sex (HR, 1.5; 95% CI, 1.0–2.2). Recipient age was inversely associated with initiation of CAV (HR, 0.8; 95% CI, 0.8–1.0). Analysis of the interaction between donor and recipient age was not significant for death ($p = 0.8$) or CAV ($p = 0.6$).

CONCLUSIONS: We found no interaction between donor and recipient age negatively affecting mortality and CAV. The identified independent risk factors may have implications for allocation strategies in elderly recipients.

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Outcomes in heart transplantation (HTX) as the preferred treatment option for terminal heart failure have been optimized constantly, and survival rates have reached approximately 85% after 1 year and 75% to 80% after 5 years.[1–4] The current median survival rate in Vienna is 87% after 1 year and 65% after 10 years. But meanwhile, conservative therapies have also improved and offer a mostly cost-effective increase of life expectancy.[5–7] Consequently, the proportion of older patients presenting for HTX has become larger, and comorbidities and the rates of previous cardiac interventions have also increased compared with the earlier eras of HTX.[4,8]

In the Eurotransplant area, donor age has risen substantially from a median of 28 years in 1990 to 42 years in 2010 (United States: 25 vs 27 years; all other

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non-European countries: 25 vs 30 years).[4] Global numbers of patients on the waiting lists have grown, which obliges transplant centers to also accept older and/or extended-criteria donor hearts.[9–11]

As an innovative strategy to more effectively widen the donor pool in kidney transplantation, the European Senior Program (ESP) was found by Eurotransplant to allocate organs from older donors to older recipients (> 65 years). Graft and patient survival was acceptable, and with this strategy, the ESP program produced superior results compared with treatment with dialysis only.[12,13]

In HTX, however, the question whether transplantation of patients older than, for example, 60 years is feasible, has not been addressed by means of such a program. Studies comparing outcome and morbidity between young and old recipients show 5-year survival rates of old recipients between 56% and 69%.[14–18] The use of organs from donors aged older than 40 years was reported, with 5-year survival rates of between 53% and 65%.[9–22] The incidence of cardiac allograft vasculopathy (CAV) was clearly associated with older donor age in a large analysis[21] and was approximately 13% after 3 years.[23] Nevertheless, matching older donors with older recipients seems to be a justifiable strategy, and currently, no hard criteria for age limits in HTX exist.[9,11,24,25]

We conducted this retrospective cohort study to elucidate interactions that are caused by the combination of donors and recipients of different ages, as described in earlier analyses in kidney transplantation.[26,27] Pre-defined possible confounders and mediator variables were adjusted for mortality and CAV after HTX. Such an analysis might provide a rational basis to improve organ allocation concerning donors and recipients of advanced age.

Methods

Design

This retrospective, observational single-center study was performed at the Medical University of Vienna. Data were prospectively collected and entered into our database. Presented data follow the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Consortium guidelines. Our patient collective consisted of 1,190 patients who underwent orthotopic HTX at our center between January 1984 and June 2011. Recipients aged younger than 16 years and re-HTX were excluded. Follow-up took place in our outpatient clinic and was complete for all patients.

Patients

The allocation strictly adhered to Eurotransplant algorithms. Four eras of transplantation were stratified:

- Era 1 (1984–1991): the program was implemented.
- Era 2 (1992–1998): donor and recipient criteria were substantially widened.
- Era 3 (1999–2002): extracorporeal membrane oxygenation support for primary graft dysfunction was initiated, and tacrolimus and mycophenolate mofetil had been introduced shortly before.
- Era 4 (2003–2011): organ availability decreased rapidly, resulting in a "high-urgency" allocation policy by Eurotransplant with rising ventricular assist device (VAD) numbers to cover the number of inotrope-dependent patients.

Immunosuppression and postoperative prophylaxis in our center have been described in detail earlier.[28] Eight endomyocardial biopsies were done during the first year or whenever indicated, and rejection grading according to International Society for Heart and Lung Transplantation (ISHLT) 1990 and 2004 criteria was applied. C4d staining was established in 2005. Coronary angiographies were performed after 1, 3, 5, 7, and 10 years, or whenever indicated. All patients diagnosed with grade CAV 1 or higher, according to ISHLT nomenclature, were counted as positive.[29]

Statistics

In descriptive analyses, continuous variables are expressed as median and interquartile range (IQR) and categoric variables as frequencies and proportions. Kaplan-Meier curves with the status indicator reversed and cumulative incidence functions were used to describe time to death and time to CAV, respectively.

Models for mortality and CAV were estimated with 3 nested sets of variables: the Basic Set included eras of transplantation and donor and recipient age per decade. Set 1 included the Basic Set and additional possible covariates and confounders such as VAD implantation, admission status, ischemic time, and donor and recipient sex. Set 2 included the Basic Set, Set 1, and possible mediator variables such as diabetes, serum creatinine, and previous cardiac surgery.[30] Other relevant variables, such as mechanical ventilation, dialysis pre-HTX, and recipient panel reactive antibody exceeding 10% accounted for less than 5% of our patient collective and were not included. A multivariable fractional polynomials algorithm was applied to model possible nonlinear relationship between continuous variables such as age.[31] The 2-way interaction between donor and recipient age was assessed in the Basic Set.

Survival analysis was performed using Cox regression models with the three nested variable sets. The risk to develop CAV was assessed using cause-specific (death-censored) Cox regression models for all time-points. For the absolute risk of donor and recipient age to develop CAV, proportional sub-distribution hazard models for competing-risk data according to Fine and Gray were applied.[32] Outcome was time to CAV, with death as the competing event. Patients who were alive without CAV at the time of their last visit were censored. Results from multivariable competing-risk regressions were described by means of sub-distribution hazard ratios (HRs) and 95% confidence intervals (CIs) and by cumulative incidence curves.

To strengthen the findings of our models using continuous age without any arbitrary cutoff, cumulative mortality and incidence of CAV were estimated for 4 hypothetical donor/recipient age combinations, with all investigated variables fixed to their median value. A p-value of < 0.05 was considered statistically significant. For statistical analysis, R 2.12 software (www.r-project.org) was used.

Results

Demographics

Patient characteristics are provided in Table 1. After exclusion of re-HTX ($n = 39$) and patients younger than 16 years ($n = 41$), 1,190 patients remained. Recipients were between16 and 73 years old, with a median age of 54 years