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Original Article

Heart Transplantation in Patients ≥ 60 Years: Importance of Relative Pulmonary Hypertension and Right Ventricular Failure on Midterm Survival

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Objectives: To determine the impact of recipient age and perioperative risk factors on midterm survival after orthotopic heart transplantation (OHT). The authors hypothesized that perioperative variables are more important as predictors of mortality than is a recipient's age.
Design: Retrospective study.
Setting: Tertiary care university hospital.
Participants: The study comprised 126 consecutive adults who underwent OHT.
Interventions: After Institutional Review Board approval, the authors analyzed 126 consecutive adult patients who underwent OHT between January 2009 and December 2015 and followed-up with them up until June 2016. Patients were divided into the following 2 groups according to the recipient's age at the time of transplantation: older group (≥ 60 y old) and younger group (18 to 59 y).
Measurements and Main Results: Actuarial survival rates for all patients were 88.1%, 78.6%, and 72.2% at 30 days, 1 year, and after a median follow-up of 18.9 months (midterm survival) (1st quartile: 8.1; 3rd quartile: 37.4), respectively. In the unadjusted analysis, the older group demonstrated a significant increase in 1-year mortality ($p = 0.005$) and a trend toward worse midterm mortality ($p = 0.087$). Multivariable analysis was performed using Cox proportional hazards regression analysis. Independent risk factors related to midterm mortality after OHT were as follows: preoperative relative pulmonary hypertension using the mean arterial-to-mean pulmonary artery pressure ratio ≤ 3 (hazard ratio [HR] 5.39, 95% confidence interval [CI] 1.64-17.74, $p = 0.006$); cardiopulmonary bypass duration (per each 10-min increment) (HR 1.14, 95% CI 1.08-1.22, $p < 0.001$); and postoperative right ventricular dysfunction (HR 3.50, 95% CI 1.52-8.05, $p = 0.003$). Neither recipients ≥ 60 years old (HR 2.15, 95% CI 0.98-4.67, $p = 0.054$) nor donor/recipient body surface area ratio (HR 1.01, 95% CI 0.98-1.04, $p = 0.463$) was an independent risk factor for midterm mortality.
Conclusions: In patients undergoing heart transplantation, survival was related more to preoperative relative pulmonary hypertension, cardiopulmonary bypass duration, and postoperative right ventricular failure than to recipient age. Older patients should be selected for OHT carefully, taking into consideration preoperative factors other than age.

Key Words: heart transplantation; perioperative; elderly; pulmonary hypertension; survival

DESPITE ADVANCES in medical and surgical therapies, including mechanical circulatory support, heart transplantation continues to be the gold standard treatment of end-stage heart

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failure. With increased life expectancy and improved heart failure care, currently there are older potential candidates for cardiac transplantation, and health centers are accepting higher-risk patients.[1] The International Society of Heart and Lung Transplantation (ISHLT) has reported that the percentage of heart transplantation patients older than 60 years has increased steadily over the last decades,[2] which is in agreement with records from the United Network for Organ Sharing (UNOS).[3] Due to limited organ availability and concerns for increased mortality, advanced age traditionally had been considered a relative contraindication for transplantation. Studies evaluating heart transplantation in older patients have yielded mixed results, with some series showing no differences in survival rates[4–20] and others reporting worse outcome among elderly patients.[3,21–28]

The issue of whether older patients should be considered equally for orthotopic heart transplantation (OHT) still is a matter of great debate. The upper age limit remains poorly defined, due in part to the high demand for transplantations and the critical shortage of donors. The ISHLT recommends that older recipients should be selected more carefully than standard candidates[29] because survival risk factors are not only a matter of age, per se. Many other risk factors have to be considered beyond chronologic age, including perioperative hazards.

This study was designed to evaluate the effects of recipient age and perioperative variables on midterm survival after OHT. The extent to which recipient age is an independent predictor of mortality when considering other perioperative variables such as the mean arterial pressure to mean pulmonary artery pressure ratio (MAP/MPAP) (relative pulmonary hypertension [PH]) and right ventricular (RV) failure is unknown. The authors hypothesized that perioperative variables are more important as predictors of mortality than is age.

Methods

Patient Population

After obtaining Institutional Review Board approval, the authors retrospectively studied all consecutive adult patients who underwent OHT between January 2009 and December 2015 at a tertiary care university hospital and followed-up with them until June 2016. Follow-up was accomplished for all patients. Patients included in the analysis had undergone OHT and were 18 years or older. Multiple organ transplantation recipients were excluded. Patients were divided into the following 2 groups according to recipient age at the time of transplantation: older group (≥ 60 y) and younger group (18 to 59 y). The recipient listing criteria were the same for all patients. The authors' program does not use an alternative list for older or so-called "marginal" donor hearts.

Data Collection

Medical records were reviewed to collect preoperative data, which included donor and recipient age, sex, height, and weight. Body surface area and body mass index were calculated using standard formulae. Anthropometric measurements of donors and recipients were correlated. History or presence of chronic renal and liver failure, diabetes mellitus, hypothyroidism, and malnutrition status (obesity and cachexia) were documented. Other relevant information, including systemic hypertension, dyslipidemia, history of stroke, anticoagulant therapy, prior cardiac surgery, or retransplantation also were recorded. Data on priority status in the recipient's waiting list (elective, urgent, or emergency) at transplantation; donor heart ischemia time; and cardiopulmonary bypass (CPB) time also were collected. Intensive care unit and hospital stay, post-transplantation echocardiographic assessment, OHT-associated complications, and mortality also were registered.

Perioperative Hemodynamic Parameters

A thermodilution pulmonary artery catheter (Edwards Lifesciences, Irvine, CA) was inserted, and a complete hemodynamic profile was obtained as part of the pretransplantation evaluation. Measured variables included systolic, diastolic, and mean pulmonary arterial pressures. The pulmonary vascular resistance was calculated as Wood units using standard formulae. Relative PH is defined by a ratio that relates MAP/MPAP. The MAP/MPAP ratio was calculated for every patient. MAP/MPAP ≤ 3 was considered as being abnormal.[30] PH secondary to left heart disease was defined as MPAP > 25 mmHg in the presence of elevated pulmonary capillary wedge pressure (> 15 mmHg) or left ventricular end-diastolic pressure (> 18 mmHg).[31] Left ventricular ejection fraction and RV function were evaluated using perioperative echocardiography. RV dysfunction was defined as tricuspid annular plane systolic excursion < 17 mm, RV fractional area change $< 35\%$, severely dilated right ventricle (RV size equal or even exceeding left ventricular dimensions), significant tricuspid regurgitation, and hypokinesia of the RV free wall.[32] Additional data such as perioperative need for a ventricular assist device and intra-aortic balloon pump also were recorded.

Statistics

Student t test or Mann-Whitney U test was used for continuous variables and Pearson chi-square or Fisher exact test for categorical variables in order to compare data from older versus younger patients. Multivariable analysis was performed using Cox proportional hazards regression analysis. Significant univariate variables and clinically relevant variables were incorporated into the multivariate models in a stepwise fashion to predict midterm mortality after OHT and to compute the hazard ratio with 95% confidence interval. Alternative models were analyzed and compared with the likelihood ratio test and Akaike information criteria values. Both criteria were used to select the best model. Unless otherwise stated, p values < 0.05 were considered to be statistically significant, and the results are expressed as mean $\pm$ standard deviation and median (interquartile range) according

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