# Elevated Heart Rate Following Heart Transplantation Is Associated With Increased Graft Vasculopathy and Mortality

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## ABSTRACT

**Background**: The effect of elevated heart rate (HR) on outcomes after heart transplantation (HT) has not been well established. The aim of this study was to assess predictors of elevated HR following HT and its impact on outcomes.

**Methods and Results**: We retrospectively evaluated 394 patients who underwent HT at 2 academic medical centers from 2005 to 2016. Patients were divided into 2 groups based on HR 1 year after HT: HR ≥95 beats/min (n = 162; 41%) and HR <95 beats/min (n = 232; 59%). Median follow-up time was 6.6 (interquartile range [IQR] 2.2−7.5) years. HR ≥95 beats/min 1 year after HT was associated with younger donor age, whereas HR <95 beats/min was associated with heavy donor alcohol use and African-American recipient race. Left ventricular (LV) end-diastolic dimension, mass, and ejection fraction were lower and E/E′ higher in the HR ≥95 group at the time of the last follow up. HR ≥95 beats/min at 1 year after HT was independently associated with the development of cardiac allograft vasculopathy and increased mortality.

**Conclusions**: HR ≥95 beats/min 1 year after HT is associated with a reduction in LV size and function, increased incidence of cardiac allograft vasculopathy, and reduced survival. Studies investigating the effect of medical HR reduction on post-HT outcomes are warranted. (*J Cardiac Fail 2019;25:249−256*)

**Key Words:** heart rate, heart transplant, cardiac allograft vasculopathy, survival.

Heart transplantation (HT) is a well established therapeutic option for patients with end-stage heart failure. Over the past few decades, advances in the field have led to a reduction in the incidence of allograft rejection and considerably improved short- to mid-term survival.[1] However, long-term complications, including cardiac allograft vasculopathy (CAV) and nonspecific graft failure, remain a challenge, and median survival after HT remains limited to ∼10.7 years.[2,3]

Cardiac denervation after HT has a variable effect on heart rate (HR), the long-term consequence of which is unclear. Elevated HR has consistently been shown to be a risk factor for adverse outcomes in the general population[4,5] as well as across the spectrum of cardiovascular disease,[4,6−9] and limited data suggest that sustained elevation in resting HR may play a role in the progression and severity of coronary atherosclerosis.[10] Previous studies evaluating the effect of elevated HR on cardiac allograft function, CAV, and mortality after HT have reported conflicting results.[11−15] Because specific HR-lowering pharmacotherapy has become available in recent years,[16] elevated HR after HT as a potential target for therapeutic intervention has gained interest.

We conducted a study to assess predictors of elevated HR 1 year after HT along with its effect on the development of cardiac allograft dysfunction, CAV, and survival.

## Methods

We performed a retrospective analysis of prospectively collected data from 506 patients who underwent HT at the University of Nebraska Medical Center (UNMC) and Loyola University Medical Center (LUMC) from January 2005 to July 2016. The study was approved by the Institutional Review Boards at both institutions.

Of the 506 patients originally reviewed, we excluded 49 that died during the first year after HT, 17 who underwent multiorgan transplantation, 12 who underwent retransplantation, 4 with a documented arrhythmia other than sinus tachycardia (ST), 7 who underwent permanent pacemaker placement, and 23 who were treated with β-blockers during the first year after HT, resulting in a study population of 394 patients (LUMC: n = 151; UNMC: n = 243). At the

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time of assessment, all patients were in sinus rhythm, without adenosine antagonist treatment, and without significant rejection or infection.

Resting HR was determined by means of electrocardiography performed 1 month, 3 months, and 1 year after HT and was assessed for every patient. Based on HR at 1 year after HT, the total cohort was divided into 2 groups: (1) HR <95 beats/min (mean HR 83 ± 8 beats/min; n = 232 [59%]); and (2) HR ≥95 beats/min (mean HR 104 ± 8 beats/min; n = 162 [41%]). HR ≥95 beats/min was defined as an elevated HR based on a previous study.[17] We chose to evaluate HR 1 year after transplantation to reduce confounders such as early sinoatrial node dysfunction, ischemic injury of the cardiac allograft, and higher rates of rejection and infections during the first year after HT.

All transplantations were performed via bicaval anastomosis.

Donor data were retrospectively obtained from United Network for Organ Sharing Donornet files and was available for all patients. Recipients' demographic and clinical data were obtained from medical records.

All UNMC patients received induction therapy with the use of basiliximab whereas induction therapy for LUMC patients was individualized based on recipient comorbidities. All patients were on a standard post-HT regimen of tacrolimus, mycophenolate mofetil, and prednisone. Prednisone was weaned as tolerated over the first 6−12 months.

Routine endomyocardial biopsies and C4D staining were performed according to the International Society of Heart and Lung Transplantation (ISHLT) recommendations.[18,19] The acute cellular rejection (ACR) score was calculated during the 12 months after HT based on the revised ISHLT grading of ACR and was normalized to the number of biopsies taken during this period in the individual patient.[20] Beginning in 2012, allomap testing replaced biopsies at 6 months after HT in stable patients with no previous history of significant rejection. Antibody-mediated rejection (AMR) was diagnosed based on positive C4D staining.[21]

Echocardiographic studies were performed and read by experienced cardiologists following standard American Society of Echocardiography recommendations.[22,23] Echocardiographic measurements were retrospectively obtained by means of chart review and were available in 325 patients (HR <95: n = 183; HR ≥95: n = 142) 1 year after HT and 233 patients (HR <95: n = 138; HR ≥95: n = 95) at their last available echocardiographic study.

Right heart catheterization studies performed by standard protocols[24] at 1 year after HT were available in 304 patients (HR <95: n = 177; HR ≥95: n = 137).

Coronary angiograms were performed and interpreted during annual evaluation for all patients. The patients' charts were reviewed to assess for the development and timing of CAV onset.

The diagnosis of CAV was made in accordance with current guidelines,[25] and patients with CAV2 and CAV3 were included in the analysis. All-cause mortality was retrospectively recorded.

### Statistical Analysis

Descriptive analysis is presented as mean ± SD for continuous data unless markedly nonnormally distributed, in which case the median with interquartile range (IQR) is used. For categoric variables, data are summarized as n (%). Univariate analysis was performed with the use of the 2-tailed *t* test for continuous data and the chi-square test for categoric data. Multivariate logistic regression analysis was used to find predictors of HR ≥95 beats/min 1 year after HT. Kaplan-Meier (KM) estimates and log-rank test were used to describe rates of CAV and survival in the study groups. Cox proportional hazard models were used to assess the effect of HR on CAV and mortality and was adjusted for all explanatory variables with $P \leq .05$ in univariate analysis. All *P* values were 2 sided and *P* values <.05 were considered to be statistically significant.

## Results

Among all of the 394 study patients, mean resting HR 1 year after HT was 92.2 ± 12.8 beats/min. Among recipients with a HR ≥95 beats/min at 1 year following HT, HR was also significantly faster at 1 month (96 ± 12 vs 87 ± 14; $P < .001$) and 3 months (96 ± 12 vs 89 ± 11; $P < .001$) after HT.

Table 1 shows donor and recipient demographics and clinical characteristics dichotomized by HR. In univariate analysis, HR ≥95 beats/min at 1 year after HT was associated with younger donor age (29.9 ± 10.9 vs 33.0 ± 11.4 years; $P = .03$) and female donors (45 [28%] vs 46 [20%]; $P = .03$). Conversely, HR ≥95 beats/min was less common in African-American recipients (16 [10%] vs 49 [21%]; $P = .01$) and in recipients that received hearts from donors with a history of heavy alcohol use (14 [9%] vs 48 [21%]; $P = .01$). The remainder of donor and recipient pre-HT characteristics did not differ between groups.

In multivariate analysis, younger donor age (odds ratio [OR] 1.33, 95% CI 1.01−4.29; $P = .05$) remained a significant predictor for HR ≥95 beats/min, and heavy donor alcohol use (OR 0.56, 95% CI 0.21−0.98; $P = .02$) and African-American recipient race (OR 0.40, 95% CI 0.19−0.85; $P = .02$) were associated with HR <95 beats/min (Table 2).

Table 3 presents recipients' clinical characteristics at 1 year dichotomized by HR. During the first year following HT, approximately one-third of patients in both groups were treated with diltiazem, whereas patients with a HR ≥95 beats/min were less likely to receive treatment with aspirin (140 [87%] vs 220 [95%]; $P = .05$). Immunosuppression, ACR score, and the incidence of AMR did not differ between groups. There was no difference in laboratory tests 1 year after HT (Table 3).

Systolic BP was lower in patients with HR ≥95 beats/min (124 ± 20 vs 132 ± 24; $P = .005$); however, it was well controlled in both groups. No differences in diastolic blood pressure or blood pressure medications were found.

**Table 1.** Donor and Recipient Demographic and Clinical Characteristics Stratified by Heart Rate (HR) at 1 Year After Heart Transplantation (HT)

| Characteristic | HR <95 (n = 232; 59%) | HR ≥95 (n = 162; 41%) | *P* Value |
|---|---|---|---|
| HR at 1 year after HT, beats/min | 83 ± 8 | 104 ± 8 | <.001 |
| Pre-transplantation characteristics | | | |
| Donor | | | |
| Donor age, y | 33.0 ± 11.4 | 29.9 ± 10.9 | .03 |
| CIT, min | 178.3 ± 50.3 | 180.9 ± 56.3 | .63 |
| Female, n (%) | 46 (20) | 45 (28) | .03 |
| Donor cause of death, n (%) | | | .27 |
| Explosive brain death | 65 (28) | 57 (35) | |
| Blunt brain trauma | 12 (51) | 73 (45) | |
| Other | 49 (21) | 32 (20) | |
| Donor/recipient BMI | 0.98 ± 0.24 | 0.98 ± 0.25 | .97 |
| Duration of CPR, min | 18.3 ± 7.4 | 23.6 ± 9.3 | .45 |
| Donor heavy alcohol use, n (%) | 48 (21) | 14 (9) | .01 |
| Donor cigarette use, n (%) | 32 (14) | 21 (13) | .74 |
| Donor history of hypertension, n (%) | 35 (15) | 23 (14) | .46 |
| Donor IV drug use, n (%) | 18 (8) | 4 (3) | .10 |
| Donor male−recipient female, n (%) | 25 (11) | 2214) | .59 |
| Recipient | | | |
| Age at transplantation, y | 50.8 ± 14.0 | 52 ± 13.4 | .50 |
| LVAD before transplantation, n (%) | 139 (60) | 73 (45) | .26 |
| Female, n (%) | 48 (21) | 35 (22) | .89 |
| Race, n (%) | | | .01 |
| White | 171 (74) | 139 (86) | |
| African Americans | 49 (21) | 16 (10) | |
| Hispanic | 3 (1.4) | 3 (1.8) | |
| Other | 6 (2.8) | 4 (2.7) | |
| Etiology of heart failure, n (%) | | | .14 |
| Ischemic cardiomyopathy | 100 (43) | 61 (38) | |
| Nonischemic cardiomyopathy | 14 (57) | 96 (59) | |
| Other | 0 | 5 (3.6) | |
| Pre-HT diabetes, n (%) | 109 (47) | 58 (45) | .72 |
| Pre-HT smoking, n (%) | 130 (56) | 85 (53) | .15 |
| Pre-HT hyperlipidemia, n (%) | 15 (66) | 94 (58) | .19 |
| Pre-HT hypertension, n (%) | 102 (71) | 164 (63) | .16 |
| Pre-HT weight (kg) | 90.1 ± 20.7 | 85.5 ± 23.2 | .12 |
| PRA class 1 | 4.4 ± 13.3 | 2.8 ± 12.4 | .46 |
| PRA class 2 | 7.4 ± 21.0 | 4.6 ± 16.4 | .36 |
| Pre-HT WBC, $10^9$/L | 8.1 ± 3.5 | 7.5 ± 23. | .17 |
| Pre-HT hemoglobin, mg/dL | 12.2 ± 2.0 | 12.2 ± 2.1 | .98 |
| Pre-HT GFR, mg/dL | 68.2 ± 27.4 | 68.6 ± 23.1 | .93 |
| Pre-HT TSH, mg/dL | 3.7 ± 1.2 | 3.9 ± 1.7 | .79 |
| Pre-HT albumin, mg/dL | 3.8 ± 0.7 | 3.6 ± 0.5 | .89 |
| Length of index hospitalization, d | 25 ± 19 | 23 ± 16 | .38 |

BMI, body mass index; CIT, cold ischemia time; CPR, cardiopulmonary resuscitation; GFR, glomerular filtration rate; IV, intravenous; LVAD, left ventricular assist device; PRA, panel reactive antibodies; TSH, thyroid-stimulating hormone; WBC, white blood cells.

Invasive hemodynamics 1 year after HT did not differ between the groups (Table 3); however, on echocardiography the recipients with HR ≥95 beats/min had a lower left ventricular end-diastolic dimension (LVDD; 4.2 ± 0.5 vs 4.4 ± 0.6; *P* = .01) and left ventricular mass (LVM; 163 ± 53 vs 180 ± 42; *P* = .04) and higher E/E′ (9.4 ± 4.1 vs 8.7 ± 3.2; *P* = .05; Table 3). This difference became more prominent at the last follow-up echocardiographic study at a median of 5.7 (IQR 2.3−7.0) years after HT (LVDD: 4.2 ± 0.5 vs 4.5 ± 0.5 [*P* < .001]; LVM: 158 ± 44 vs 189 ± 59 [*P* < .001]; E/E′: 9.5 ± 3.8 vs 8.9 ± 3.2 [*P* = .03] in the HR ≥95 group and HR <95 groups, respectively). Although there was no difference between groups in left ventricular ejection fraction (LVEF) 1 year after HT (58 ± 7.2 vs 59 ± 6.7; *P* = .38), LVEF was lower in the HR ≥95 group on the last follow-up echocardiogram (55 ± 5.2 vs 59 ± 7.1; *P* = .03).

**Table 2.** Predictors of Elevated Heart Rate at 1 Year After Heart Transplantation (Logistic Regression)

| Factor | Odds Ratio | 95% CI | *P* Value |
|---|---|---|---|
| Donor age, y | 1.33 | 1.01−4.29 | .05 |
| Donor heavy alcohol use | 0.56 | 0.21−0.98 | .02 |
| Female donor | 0.87 | 0.65−1.47 | .65 |
| African-American recipient | 0.40 | 0.19−0.85 | .02 |

CI, confidence interval.

### Cardiac Allograft Vasculopathy

Overall, 91 (23%) patients developed CAV2 (n = 64) or CAV3 (n = 27) during a median follow-up of 6.6 (IQR 2.2−7.5) years. Freedom from CAV2 or CAV3 in patients

**Table 3.** Recipients Clinical Characteristics at 1 Year After Heart Transplantation (HT) Stratified by Heart Rate (HR) at 1 Year After HT (n = 394)

| Characteristic | HR <95(n = 232; 59%) | HR ≥95(n = 162; 41%) | *P* Value |
|---|---|---|---|
| Medical treatment 1 year after HT | | | |
| Aspirin, n (%) | 220 (95) | 140 (87) | .05 |
| Diltiazem, n (%) | 84 (36) | 55 (34) | .83 |
| Hydralazine, n (%) | 27 (12) | 13 (8) | .21 |
| ACE inhibitor, n (%) | 88 (38) | 64 (40) | .83 |
| Spironolactone, n (%) | 12 (5) | 13 (8) | .31 |
| CNI, n (%) | 20 (89) | 13 (84) | .23 |
| Sirolimus, n (%) | 37 (16) | 17 (11) | .60 |
| Mycophenolate, n (%) | 192 (83) | 136 (84) | .86 |
| Azathioprine, n (%) | 13 (6) | 9 (6) | .83 |
| Rejection 1 year after HT | | | |
| ACR score | 0.48 ± 0.31 | 0.48 ± 0.30 | .92 |
| AMR, n (%) | 35 (15) | 31 (19) | .68 |
| Laboratory findings 1 year after HT | | | |
| WBC, $10^9$/L | 6.8 ± 2.6 | 6.6 ± 3.5 | .67 |
| Hemoglobin, mg/dL | 13.1 ± 1.6 | 12.8 ± 1.9 | .12 |
| Platelets count, $10^9$/L | 107 ± 57 | 197 ± 104 | .98 |
| Creatinine, mg/dL | 1.7 ± 1.9 | 1.6 ± 1.8 | .64 |
| Bilirubin, mg/dL | 0.8 ± 0.4 | 0.9 ± 1.2 | .47 |
| Albumin, mg/dL | 3.9 ± 0.4 | 3.9 ± 0.5 | .63 |
| TSH, U/mL | 2.0 ± 1.2 | 1.9 ± 1.7 | .79 |
| Hemodynamics 1 year after HT | (n = 177) | (n = 137) | |
| Systolic BP, mm Hg | 132 ± 24 | 124 ± 20 | .005 |
| Diastolic BP, mm Hg | 80 ± 113 | 80 ± 13 | .95 |
| Mean RAP, mm Hg | 7.1 ± 4.5 | 7.9 ± 10.5 | .42 |
| PCWP, mm Hg | 12.4 ± .15 | 12.4 ± 5.8 | .93 |
| Mean PA, mm Hg | 21 ± 6 | 22 ± 7 | .32 |
| Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$ | 3.1 ± 0.6 | 3.2 ± 0.8 | .30 |
| Echocardiography 1 year after HT | (n = 183) | (n = 142) | |
| EDST (cm) | 1.2 ± 0.2 | 1.1 ± 0.2 | .40 |
| EDPWT (cm) | 1.1 ± 0.2 | 1.1 ± 0.3 | .13 |
| LVDD (cm) | 4.4 ± 0.6 | 4.2 ± 0.5 | .01 |
| LVM | 180 ± 42 | 163 ± 53 | .04 |
| RWT | 0.51 ± 0.14 | 0.55 ± 0.15 | .10 |
| LVEF (%) | 59 ± 6.7 | 58 ± 7.2 | .38 |
| E/E′ | 8.7 ± 3.2 | 9.4 ± 4.1 | .05 |
| RVDD (cm) | 3.5 ± 0.5 | 3.4 ± 0.5 | .38 |
| TR ≥ grade II, n (%) | 16 (9) | 13 (9) | .78 |

ACE, angiotensin-converting enzyme; ACR, acute cellular rejection; AMR, antibody-mediated rejection; BP, blood pressure; CNI, calcineurin inhibitor; EDPWT, end-diastolic posterior wall thickness; EDST, end-diastolic septum thickness; LVEF, left ventricular ejection fraction; LVDD, left ventricular end-diastolic dimension; LVM, left ventricular mass; RVDD, right ventricular diastolic dimension; PCWP, pulmonary capillary wedge pressure; PA, Pulmonary artery; RAP, right atrial pressure; TR, tricuspid regurgitation; WBC, white blood cells.

with HR <95 beats/min was 82%, 79%, and 56% compared with 80%, 64%, and 40% in the HR ≥95 beats/min group at 3, 5, and 10 years after HT, respectively ($P = .004$; log-rank), with separation of the Kaplan-Meier curves starting ~3 years after HT (Fig. 1).

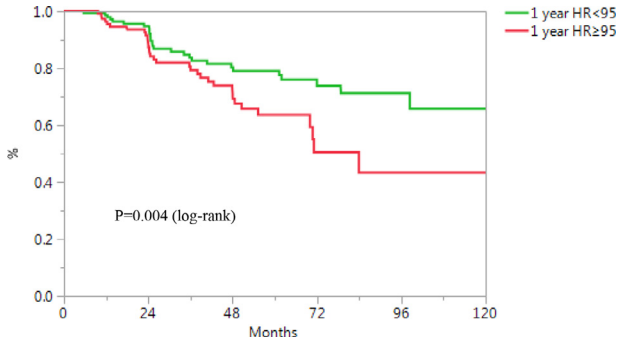


**Fig. 1.** Heart rate at 1 year after heart transplantation and freedom from cardiac allograft vasculopathy.

In adjusted Cox proportional regression analysis, elevated HR at 1 year after HT analyzed either as a continuous variable (hazard ratio 1.03, 95% CI 1.01−1.06; $P = .02$) or as a categoric variable (HR ≥95; hazard ratio 2.7, 95% CI 1.4−5.6; $P = .005$) was associated with increased risk of CAV. Older donor age (hazard ratio 1.06, 95% CI 1.01−1.11; $P = .013$) and lack of aspirin treatment (hazard ratio 4.9, 95% CI 1.33- 25.13; $P = .014$) were other predictors of CAV development (Table 4).

## Survival

During the median 6.6 (IQR 2.2−7.5) years of follow-up, 47 (12%) patients died. The survival rate was significantly lower in the HR ≥95 group compared with the HR <95 group: 98%, 96%, and 87% vs 93%, 84%, and 74% ($P = .009$; log-rank) at 3, 5, and 10 years after HT, respectively. The Kaplan-Meier curves separated early, with the differences becoming more pronounced over time (Fig. 2).

**Table 4.** Risk Factors for Cardiac Allograft Vasculopathy: Adjusted Cox Proportional Hazard Models

| Factor | Hazard Ratio | 95% CI | *P* Value |
|---|---|---|---|
| Donor age, y | 1.06 | 1.01–1.11 | .013 |
| HR, beats/min | 1.03 | 1.01–1.06 | .02 |
| E/E′ | 1.04 | 0.96–1.11 | .35 |
| Systolic BP at 1 year, mm Hg | 0.98 | 0.96–1.00 | .09 |
| LVM at 1 year, g | 1.00 | 0.99–1.01 | .20 |
| Donor heavy alcohol use | 0.54 | 0.18–1.47 | .23 |
| Lack of aspirin treatment | 4.9 | 1.33–25.13 | .014 |

Abbreviations as in Tables 1–3.

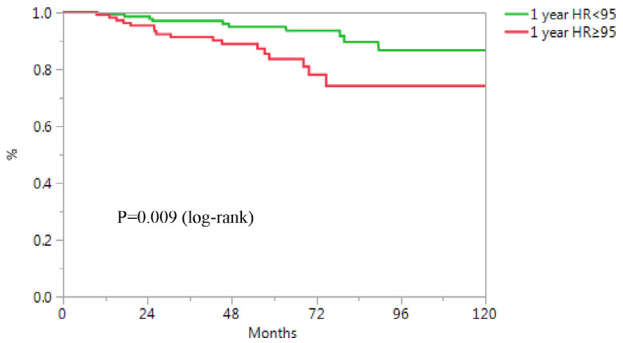


**Fig. 2.** Heart rate at 1 year and survival after heart transplantation.

In adjusted Cox proportional regression analysis, HR analyzed as a continuous variable (hazard ratio 1.08, 95% CI 1.01–1.15; $P = .02$) and as a categoric variable (hazard ratio 3.9, 95% CI 1.4–7.7, $P = .004$) was independently associated with increased risk of mortality (Table 5).

## Discussion

This study represents the largest evaluation of the relationship between HR and survival after HT in the contemporary era. The primary findings were that patients with HR ≥95 beats/min 1 year after HT had decremented LV size and function and are at increased risk for development of late CAV and mortality. Although the retrospective nature of the study precludes an assessment of causality, the association itself is important because CAV and nonspecific allograft failure are leading causes for late morbidity and mortality in this population, and specific HR-lowering pharmacotherapy is now available.

**Table 5.** Risk Factors for Mortality After Heart Transplantation: Adjusted Cox Proportional Hazard Models

| Factor | Hazard Ratio | 95% CI | *P* Value |
|---|---|---|---|
| Donor age, y | 1.04 | 0.94–1.14 | .47 |
| HR at 1 year after HT, beats/min | 1.08 | 1.01–1.15 | .02 |
| E/E′ | 1.12 | 0.97–1.27 | .12 |
| Systolic BP at 1 year, mm Hg | 1.00 | 0.96–1.04 | .94 |
| LVM at 1 year, g | 1.00 | 0.98–1.01 | .98 |
| Donor heavy alcohol use | 0.37 | 0.04–25.9 | .90 |
| Lack of aspirin treatment | 1.80 | 0.01–33.6 | .06 |

Abbreviations as in Tables 1–3.

Cardiac denervation after HT has a variable effect on HR, with post-HT ST attributed to disruption of autonomic innervation of the cardiac allograft and independent functioning of the allograft ganglia.[26] A lack of presynaptic neuronal uptake causes a shift from β1 to β2 receptor expression in the myocardium and increases cardiac allograft response to circulating catecholamines.[27,28] Importantly, it is known from the nontransplant population that prolonged exposure to circulating plasma catecholamines has multiple deleterious cardiac effects.[29]

### Predictors of Elevated Heart Rate 1 Year After HT

Our study revealed a number of predictors of elevated HR 1 year after transplantation. First, in agreement with previous reports,[13,14,17] our study showed that elevated resting HR after HT was associated with younger donor age, a finding best explained by up-regulation of β1-adrenergic receptors and increased cardiac muscle sympathetic nerve activity in youth.[30] Younger recipient age, on the other hand, is associated with increased availability of target-derived neurotrophic factors and enhanced allograft reinnervation;[31] unfortunately, changes in HR after the first year after transplantation was beyond the scope of the present study. Second, donor alcohol abuse was associated with slower HR after transplantation, a novel finding that may represent alcoholic damage to the donors' sinus node and decreased sensitivity of the cardiac allograft to circulating catecholamines.[32] This hypothesis is supported by experimental data that demonstrated a direct toxic effect of alcohol to the sinus node.[33] Third, African-American recipient race also was associated with slower HR at 1 year in both univariate and multivariate analysis. The physiologic mechanism underlying this novel finding is unclear. Finally, patients with elevated resting HR at 1 year also had significantly faster HR at both 1 and 3 months after HT, so although the 1-year time point was chosen in this study to reduce confounders, such as early sinoatrial node dysfunction, ischemic injury of the cardiac allograft, and higher rates of rejection and infections during the early post-HT period, patients with elevated HR and potentially worse long-term prognosis might be identified at an earlier time point.

### Heart Rate and Cardiac Allograft Function

In line with previous data, our study showed that elevated HR after HT is associated with a decrease in LVDD, shortened diastolic filling time, and decreased LVM.[34,35] In addition, patients with HR ≥95 had a significantly higher E/E′ on 1-year and later echocardiography, which is consistent with impaired cardiac allograft diastolic function. Furthermore, whereas cardiac allograft systolic function as measured by means of LVEF on echocardiography 1 year after HT remained normal, it declined on the last available echocardiography with a median of 5.7 years follow up in the HR ≥95 group.

### Heart Rate and Cardiac Allograft Vasculopathy

CAV is a unique form of accelerated atherosclerosis resulting from a complex interplay between immunologic and nonimmunologic factors.[36] Although compelling experimental and clinical evidence shows that sustained HR elevation plays an important role in the pathogenesis of native artery atherosclerosis,[10] the data regarding the role of HR in CAV are limited and conflicting. An early HT study suggested that the prevalence of CAV is higher in patients with lower HR;[37] however, a postmortem study revealed a link between sudden cardiac death and elevated HR.[38] More recently, Olmetti et al found that elevated HR was a univariate predictor of CAV; however, on multivariate analysis only donor age and time after HT were predictive of CAV development.[14]

In our study, HR was independently associated with a 3% increase in the rate of CAV per point increase in HR beats/min, and HT recipients with HR ≥95 beats/min were 2.7 times more likely to develop CAV than those with HR <95 beats/min. Moreover, the separation of the Kaplan-Meier curves started 3 years after HT, suggesting a significant effect of post-HT ST on late CAV development. An assessment of the relationship between HR and CAV severity was not possible because of the relatively small number of patients in this study that developed CAV3.

Although older donor age is a well established risk factor for CAV development,[39] and preexisting donor coronary artery disease can serve as a starting point for early CAV, the impact of donor atherosclerosis on late CAV progression remains controversial, and several studies found no difference in the rate of intimal thickening between patients with and without preexisting donor coronary artery disease.[40–42] One suggested mechanism for the late development of CAV is pronounced coronary epicardial endothelial dysfunction with impairment of the endothelial nitric oxide synthase pathway and decreased basal nitric oxide activity or synthesis in transplant recipients with ST.[43] Notably, pharmacologic HR reduction therapy has been shown to improve endothelial function of the native coronary arteries in the nontransplant population,[44] although the effect of HR-lowering treatment on endothelial function and CAV development in the HT population has not yet been studied.

### Heart Rate and Survival

The relationship of elevated HR after HT and survival has been previously studied with conflicting results.[11–13,15,45,46] In a single-center retrospective study of 78 patients, Anand et al found resting HR >90 beats/min at 3 months after HT was predictive of early mortality (hazard ratio 2.8, 95% CI 1.5−5.1; $P < .0013$),[11] and in a multicenter study of 312 HT patients in Spain, Castel et al found resting HR ≥90 beats/min at 1 year after transplantation was associated with lower survival rates at 3, 5, and 10 years.[12] Similarly, Barge-Caballero et al found elevated HR to be a risk factor for all-cause mortality (hazard ratio 1.058, 95% CI 1.030−1.087 based on continuous HR),[45] and in a single-center cohort of 493 patients transplanted from 1987 to 2010 Ciarka et al found that higher HR and nonuse of β-blockers were independently associated with higher mortality.[15] Finally, a single-center retrospective study of 191 HT recipients by Melero-Ferrer et al found worse survival among patients with an elevated HR one year following transplant.[46] In contrast, Shah et al performed a large single-center study evaluating 544 HT recipients from 1994 to 2008 and found no effect of elevated HR on 5-year survival.[13]

Results of our study suggest that a HR <95 beats/min conferred a significant long-term survival benefit, and patients with HR ≥95 beats/min were 3.9 times more likely to die than those with HR <95 beats/min during the median follow-up of 6.6 years. In contrast to previous data, our study included HT recipients from the contemporary transplant era with bicaval techniques and longer follow-up. Furthermore, in contrast to previous studies, no patients included in our study were treated with β-blockers.

Our study suggested a relationship between aspirin use and outcomes. The information on the effect of antiplatelet treatment on the course and outcomes of CAV is limited and contradictory,[47,48] and there are no formal recommendations for aspirin therapy after HT. Therefore, the decision to start early aspirin treatment is generally made by the transplant cardiologist based on donor (older age, presence of atherosclerosis) and recipient (ischemic cardiomyopathy, vascular disease, conventional risk factors for atherosclerosis) characteristics. In our study, recipients with HR ≥95 beats/min showed trends toward lower incidence of pre-transplantation hypertension and hyperlipidemia and received hearts from significantly younger donors; these observations may explain why these same patients were also less likely to be taking aspirin at 1 year after transplantation. The finding that lack of aspirin use was an independent predictor for CAV and trended toward worse overall survival is noteworthy, and larger studies and/or clinical trials to further investigate the potential benefit of aspirin after HT are warranted.

### Treatment

Current ISHLT guidelines do not recommend medical treatment for HR reduction.[19] Although β-blockers slow HR in transplanted hearts, their use in this population is controversial. Although one large single-center study found β-blockers to be independently associated with better post-transplantation survival,[15] several earlier studies raised concerns about their effect on exercise capacity.[49,50] Diltiazem, a calcium-channel blocker commonly used for blood pressure control after HT[51] despite its significant drug-drug interactions with calcineurin inhibitors, also lowers HR, may prevent the progression of CAV[52] and improve exercise capacity,[53] and has been retrospectively linked to fewer episodes of sepsis in diabetic recipients of kidney transplants treated with cyclosporine.[54] Notably, there was no difference in diltiazem treatment between groups in our

study. Finally, none of the patients in the present study were receiving ivabradine, a novel $I_f$-channel blocker that selectively slows sinus node depolarization and resultant HR. Ivabradine has recently been pursued in HT recipients and reported to be safe and effective in alleviating ST,[55] and a recent study by Rivinius et al[16] showed improved survival in HT recipients treated with ivabradine compared with β-blockers, a finding suggesting a causal link between HR and survival after HT.

## Study Limitations

This study was limited primarily by its retrospective design. Although elevated HR 1 year after HT maintains statistical significance after multivariate adjustment, this finding may be an epiphenomenon reflecting differences in donor age, sympathetic activity, or other confounding factors. It also should be recognized that increased HR may be a risk factor for poor prognosis, rather than a primary contributor to CAV and mortality in HT patients; to show causality would require further and more robust evidence that a specific HR-lowering intervention improves outcome in HT recipients. The other limitation is that determination of elevated HR for this study was based on a single resting electrocardiographic recording performed 1 year after HT; however, HR was also significantly higher at 1 and 3 months in the HR ≥95 group, and HR variability is lowest during the first year following HT.[56]

## Conclusion

HT recipients with resting HR ≥95 beats/min have worse LV systolic and diastolic function and higher rates of CAV and mortality than those with lower resting HR. Whether pharmacologic lowering of HR would result in improvement of late-term outcomes in HT recipients warrants further investigation.

## Disclosures

None.

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