

Editorial

Slowing Sinus Tachycardia in Heart Transplant Recipients: Is It Time?



Reducción de frecuencia en la taquicardia sinusal en pacientes con trasplante cardiaco: ¿ha llegado el momento?

Kambiz Ghafourian and Jon A. Kobashigawa*

Cedars Sinai Heart Institute, Los Angeles, California, United States

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In the article published in *Revista Española de Cardiología*, Barge-Caballero et al¹ report on the results of a single-center retrospective observational study to explore the prognostic significance of the mean resting heart rate (HR) at 1 year after heart transplantation and its temporal trend. The authors concluded that elevated resting HR after heart transplantation is a poor prognostic marker, being associated with increased mortality. This topic is of keen interest to the field of heart transplantation particularly as it questions whether HR slowing medications may be of value for patients with sinus tachycardia.

The “resting HR” in the intact heart is predominately determined by vagal influence and hence it is slower than the intrinsic HR. The “intrinsic HR” refers to the HR following complete pharmacologic blockade of the cardiac autonomic system; it has been shown to be related to age, physical fitness and probably to the overall state of health of the myocardium.² Over the past few decades, several epidemiological studies have shown an association between elevated resting HR in the intact heart and all-cause and cardiovascular mortality in the general population, as well as in groups with various cardiovascular diseases.^{3–5} Also, inference from clinical trials has suggested that the mortality benefit from beta-blocker use in patients with acute myocardial infarction or heart failure is at least in part related to the drug-mediated reduction in the resting HR.⁵ More recently, novel pharmacologic intervention with the drug ivabradine has targeted elevated resting HR as a modifiable cardiovascular risk factor with promising results.⁶

In heart transplantation, transection of the autonomic fibers during transplant surgery has 2 major outcomes: *delayed and blunted HR response to exercise* due to sympathetic denervation, and *elevated resting HR* due to vagal denervation. The “normal” range of resting HR in heart transplant recipients is not clearly defined but generally a value between 90 and 110 beats per minute (bpm) is considered acceptable.⁷ The relevant unanswered questions in heart transplantation include: a) is the elevated resting HR an

independent risk factor for poor outcomes? and, more importantly, b) could interventions targeted at reducing HR improve outcomes?

The notion that elevated resting HR in heart transplant recipients could be associated with poor clinical outcomes is not new. Several small, observational and retrospective studies have shown such an association. Anand et al⁸ performed a retrospective observational study of 78 heart transplant recipients at Ochsner Clinic Foundation. These authors found that HR > 90 bpm at 3 months post-transplant was a significant predictor of early mortality as early as 9 months after transplantation (hazard ratio[HR] = 2.8; 95% confidence interval [95%CI], 1.5–5.1; $P < .0013$). They also showed that recipients with a net increase in HR over the 10-year follow-up were 4.7 times more likely to die than those whose HR was unchanged or decreased over time (95%CI, 1.9–12).

In another retrospective study, Castel et al⁹ evaluated 312 patients who underwent heart transplantation in 2 transplant centers in Barcelona. During a mean follow up of 5.5 years, recipients with a mean HR ≥ 90 bpm at 1 year after transplantation had a significantly higher risk of all-cause mortality (HR = 2.4; 95%CI, 1.2 to 4.5; $P = .009$) and this was mainly driven by the mortality related to cardiac allograft vasculopathy (CAV). In a multivariate analysis, the resting HR at 1-year post-transplant was an independent predictor of all-cause mortality (HR = 3.2; 95%CI, 1.4–7.1; $P = .004$). Likewise, Melero-Ferrer et al¹⁰ analyzed the data from 191 heart transplant recipients in their center and found that the resting HR at 1-year post-transplant was an independent predictor of mortality. In a multivariate model, baseline HR, CAV and donor age were independent predictors of long-term survival.

These and a few other studies suggest an association between elevated resting HR and poor clinical outcomes in heart transplant recipients. However, the validity and generalizability of the findings are limited by concerns about the sample size, study design, data analysis and the retrospective and observational design of these studies. Moreover, other studies have yielded

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* Corresponding author: 127 South San Vicente Blvd., Suite A3107, Los Angeles, CA 90048, United States.

E-mail address: Jon.Kobashigawa@cshs.org (J.A. Kobashigawa).

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contradictory findings, particularly with regard to the association between resting HR and CAV.

In a single-center study from France, Ambrosi et al¹¹ analyzed data from 143 heart transplant recipients. On routine coronary angiography, 56 patients were found to have coronary lesions and 87 had angiographically normal coronary arteries. Mean resting HR measured at 3 months post-transplant did not differ between these 2 groups (96.4 vs 98.3 bpm; $P = .34$). Survival without coronary lesions also was not significantly different between patients with basal HR $\leq$ or > 97 bpm ($P = .44$).

Gullestad et al¹² analyzed intravascular ultrasound data from 130 heart transplant recipients at Stanford. Surprisingly, CAV was more common in recipients with slower HR (49% vs 33%; $P < .05$). However, donor age was higher in these recipients. On multivariate regression analysis, only donor age and years after transplantation were independently correlated with CAV. The authors concluded that CAV is more common in recipients with slower HR but suggested that this may reflect impaired blood flow to sinoatrial node in the older-age donor hearts.

In another retrospective study, Olmetti et al¹³ reported on the outcomes of 244 heart transplant recipients in a single center in Italy. Similar to the findings by Gullestad et al., CAV was associated with the donor age, which was higher in the recipients with slower HR. On multivariate analysis, only donor age, chronic renal failure and left ventricular end-diastolic wall thickness were significant predictors of CAV. These authors concluded that the elevated resting HR in heart transplant recipients reflected *intrinsic* HR and was a simple epiphenomenon of the donor's age. Our group also analyzed data of 544 heart transplant recipients in our center and found that mean first-year HR did not provide prognostic significance for 1-year freedom from treated rejection, 5-year survival or the development of CAV 5 years after transplantation.¹⁴

There are several concerns with the current study by Barge-Caballero et al. These authors found that donor age was the only baseline clinical variable showing a significant correlation with baseline HR ($r = -0.253$; $P = .001$). This finding is consistent with previous studies showing an elevated resting HR in the recipients of younger donor hearts. However, several other important factors could affect the resting HR after heart transplantation that were not included for the analysis in this study. For example, donor-recipient sex mismatch, as well as donor-recipient size mismatch could affect the resting HR after heart transplantation. Variables such as weight, height, body mass index, and left ventricular mass index are particularly relevant with regard to size matching between donors and recipients.

Other than baseline characteristics, events during the first year after transplantation could impact the mean HR at the end of the first year. For example, factors such as hemodynamically-significant allograft rejection, persistently reduced left ventricular ejection fraction or episodes of infection during the first year could affect the mean resting HR. These factors could also impact long-term survival after heart transplantation and function as confounder variables.

Lastly, CAV could be associated with elevated resting HR, as well as transplant survival. However, assessment of CAV in this study was suboptimal. Routine coronary angiography was only performed during the last 2 years of the 10-year study period. In addition, CAV was not included in the multivariate analysis.

Some of the limitations of the current study are merely due to its retrospective and observational design, while others are

due to the fact that so many known and unknown confounders could be associated with both resting HR and outcomes after heart transplantation. Controlling for all these factors in a retrospective and observational study is very difficult. Questions remain if the elevated resting HR in heart transplant recipients is indeed an independent risk factor for poor outcomes.

All of the published studies that intended to answer this question have significant limitations and have produced inconsistent and, at times, contradictory findings. It is very unlikely that conducting another retrospective observational study in the future, even with a flawless design, could shed more light and provide a definitive answer to this question. However, we believe that the current evidence in the literature provides an adequate signal of harm that justifies further research. Probably a more important question to answer is: does reducing the elevated resting HR after heart transplantation improve outcomes?

Ivabradine is a first-in-class inhibitor of the “funny” current (I_f) that regulates the pacemaker activity of the sinoatrial node and has specific HR-reducing properties. Early evidence suggests the safety of this medication in heart transplant recipients and its potential benefits by reducing left ventricular mass index.^{15,16} If pharmacologic interventions such as ivabradine lead to improved clinical outcomes in heart transplantation, the above-mentioned unanswered question could be answered with more convincing evidence.

CONFLICTS OF INTEREST

None declared.

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