Brief Report

Be Still My Beating Heart: Should Heart Rate Be a Target of Therapy After Heart Transplantation?

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The presence of an elevated resting heart rate (HR) is a well appreciated phenomenon in patients after heart transplantation. The mechanism of tachycardia relates to loss of vagal input to the sinoatrial (SA) node as a consequence of cardiac denervation. As such, this can be viewed as a version of inappropriate sinus tachycardia. Patients are generally told to regularly monitor heart rate and blood pressure after transplantation, but unlike blood pressure it is often unclear what HR warrants treatment and if so with what agents. There is also wide variability in clinical practice regarding post-transplantation HR assessment and management, particularly regarding the use of β-blockers. Patients themselves are frequently told that having a high pulse rate is just an inevitable consequence of heart transplantation and often stop monitoring or worrying about HR after the first few months. For these reasons, it remains critical to evaluate whether treating an elevated HR improves post-transplantation outcomes.

In patients with systolic heart failure there is compelling evidence that elevated HR is associated with worse outcomes, and that decreasing HR with the use of β-blockers or ivabradine can improve cardiovascular prognosis.[1,2] This may or may not also be true in patients with diastolic heart failure.[3] Whether the same tenet holds for patients with normal LV function after heart transplantation remains less clear. Several single-center retrospective studies have suggested that elevated HR is associated with adverse post-transplantation outcomes, including exercise intolerance, mortality, and graft loss.[4,5] However, variable use of β-blockers and differences in study design (variable definitions of elevated HR, timing of HR assessment after transplantation, etc) cast some doubt on the generalizability of these findings. The relationship between elevated HR and coronary artery vasculopathy remains even more uncertain. Although a resting HR >90 beats/min was determined to be an independent predictor of mortality and cardiac allograft vasculopathy (CAV) in one study,[6] it has also been reported that CAV is more common in those patients with slower HR, a finding which may have been related to older donor age.[7] Another well conducted study revealed no relationship between HR at 1 year and survival or CAV prevalence at 5 years.[8]

In the current issue of the *Journal*, Leibo et al provide new data on the relationship between HR, CAV, and mortality in a relatively large 2-center post-transplantation patient population. For this study, heart transplant recipients were divided into 2 cohorts based on whether their resting HR at 1 year was greater than or less than 95 beats/min. This value happened to be roughly the median HR at 3 months for the study cohort and was chosen based on an earlier study showing HR ≥95 at 3 months after heart transplantation was associated with reduced exercise tolerance in stable heart transplant recipients. The primary outcomes were post-transplantation survival and CAV prevalence, with an average patient follow-up at the time of analysis of 6.6 years. The primary findings were that recipients with a resting HR >95 beats/min had decreased long-term survival and more frequent development of moderate or severe CAV (CAV2 or CAV3). Importantly, immunosuppressive regimens, surgical technique, donor age, and the incidence of cellular or antibody-mediated rejection were not different between the groups. These observations are consistent with a recent report from Barge-Caballero et al and add to a growing body of evidence that elevated HR has a detrimental impact on post-transplantation outcomes.[9]

Although this study was well designed, there are some issues that require further consideration. There were no patients on β-blockers in the study cohort, which may not be reflective of management practice at other institutions. Moreover, the reported changes in left ventricular (LV) dimension were curious. Those with elevated HR tended to have smaller LV cavity size and lower LV mass. Based on these data, it is tempting to speculate that elevated HR may occur as a

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See page 258 for disclosure information.

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consequence of lower stroke volume. However, this is not consistent with the fact that treatment directed to lower HR often reduces LV mass (see below). The authors do not postulate a potential mechanism, but this observation suggests that other physiologic differences may exist between these patients in addition to HR. The study by Leibo et al used an HR cutoff of 95 beats/min, and previous studies have used values from ranging from 90 to 105 beats/min as cutoff points for analyzing outcomes. As such, it remains somewhat unclear at what HR threshold the risk of adverse outcomes starts to increase. It should also be noted that CAV status in this study was defined by retrospective assessment of annual coronary angiography reports. Given the potential variability between readers and the lack of sensitivity of angiography, the use of blinded reviewers of the primary data could have provided superior data.

In light of the findings of this study along with others in the literature, a compelling argument can be made that elevated HR is a risk factor for worse long-term outcomes after transplantation. However, even if we accept this association, the real question is whether treating elevated HR decreases these risks. In the current era, the options for treating elevated HR include traditional agents such as β-blockers (metoprolol, carvedilol) and calcium-channel blockers (diltiazem) as well as the more recently available ivabradine. Although the use of β-blockers was once discouraged after transplantation because of concerns of exercise intolerance, it is now considered to be reasonable to use β-blockers in practice. Moreover, there is clinical evidence that metoprolol can decrease HR in patients after transplantation[10] and retrospective data suggest that β-blockers use after transplantation is associated with improved survival.[11] Whether this is related to the central or cardiac-specific effects of adrenergic blockade remains unclear. Moreover, there are no randomized studies of transplantation outcomes on patients taking β-blockers.

Ivabradine is an inhibitor of the I*k* funny current that controls activation of the SA node, making it a selective regulator of HR. As a consequence, ivabradine is an attractive agent to consider for management of the inappropriate sinus tachycardia that occurs after transplantation. In a small study of heart transplant recipients, ivabradine more potently reduced HR and was better tolerated than metoprolol.[12] Moreover, retrospective data comparing ivabradine with metoprolol demonstrated reduced LV mass and improved survival in patients receiving ivabradine.[10] That same group of investigators has also shown that the reduction in LV mass seen after 12 months on the drug is sustained up to 3 years while on treatment.[13,14] Collectively, the results with ivabradine provide encouraging evidence that this medication is well tolerated and may have sustained beneficial effects on LV remodeling and perhaps post-transplantation survival. Moving forward, the study by Liebo et al combined with previous literature supports the need for an adequately powered clinical trial of ivabradine in patients after heart transplantation. However, there are several key factors to consider for such a study, including HR cutoffs for enrollment, timing of HR assessment for enrollment (3−12 months?) and initiation of therapy, need to incorporate or exclude β-blockers, and definition of relevant clinical outcomes (eg, survival, CAV with angiography or intravenous ultrasound, exercise tolerance). Ultimately, we owe it to our patients to address this question in a definitive fashion so that we can maximize the likelihood of long-term survival.

Disclosures

None.

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