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Original article

Prognostic Significance of Heart Rate and its Long-term Trend in Cardiac Transplant Patients

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ABSTRACT

Introduction and objectives: The aim of the present study was to examine the prognostic significance of heart rate and its trend in heart transplantation.
Methods: This observational study enrolled 170 patients who received a bicaval heart transplant between 1995 and 2005; all were in sinus rhythm. The resting heart rate was determined via electrocardiography at the end of the first posttransplant year and annually until the tenth year. Cox analysis was used to evaluate the incidence of adverse events with a mean (standard deviation) follow-up of 8.9 (3.1) years. The primary study end point was the composite outcome of death or graft dysfunction.
Results: The resting heart rate at the end of the first posttransplant year was an independent predictor of the primary composite end point (hazard ratio = 1.054; 95% confidence interval, 1.028-1.080; $P < .001$) and was significantly associated with total mortality (hazard ratio = 1.058; 95% confidence interval, 1.030-1.087; $P < .001$) and mortality from cardiac causes (hazard ratio = 1.069; 95% confidence interval, 1.026-1.113; $P = .001$), but not with graft dysfunction (hazard ratio = 1.028; 95% confidence interval, 0.989-1.069; $P = .161$). For patients with a heart rate ≥ 105 or < 90 bpm vs those with 90-104 bpm, the hazard ratios of the primary end point were 2.233 (95% confidence interval, 1.250-3.989; $P = .007$) and 0.380 (95% confidence interval, 0.161-0.895; $P = .027$), respectively. Heart rate tended to decrease in the first 10 years after transplantation ($P = .001$). Patients with a net increase in heart rate during follow-up showed a higher incidence of adverse events.
Conclusions: An elevated heart rate is an adverse prognostic marker after heart transplantation.

Significado pronóstico y evolución a largo plazo de la frecuencia cardiaca en los pacientes con trasplante cardiaco

Palabras clave:
Trasplante
Pronóstico
Frecuencia cardiaca

RESUMEN

Introducción y objetivos: Estudiar la evolución y el significado pronóstico de la frecuencia cardiaca tras el trasplante cardiaco.
Métodos: Estudio observacional de 170 pacientes que recibieron un trasplante cardiaco bicavo entre 1995 y 2005; todos estaban en ritmo sinusal. La frecuencia cardiaca en reposo se determinó a partir de electrocardiogramas al final del primer año tras el trasplante y anualmente hasta el décimo año. Mediante análisis de Cox, se evaluó la incidencia de eventos adversos en un seguimiento medio de 8,9 ± 3,1 años. El evento principal del estudio fue la variable combinada muerte o disfunción del injerto.
Resultados: La frecuencia cardiaca en reposo, medida al final del primer año tras el trasplante, fue un predictor independiente del evento combinado principal (*hazard ratio* = 1,054; intervalo de confianza del 95%, 1,028-1,080; $p < 0,001$). Se observó una asociación estadísticamente significativa con la mortalidad total (*hazard ratio* = 1,058; intervalo de confianza del 95%, 1,030-1,087; $p < 0,001$) y con la mortalidad por causas cardiacas (*hazard ratio* = 1,069; intervalo de confianza del 95%, 1,026-1,113; $p = 0,001$), pero no con la disfunción del injerto (*hazard ratio* = 1,028; intervalo de confianza del 95%, 0,989-1,069; $p = 0,161$). Para los pacientes con frecuencia cardiaca ≥ 105 y < 90 lpm frente a aquellos con 90-104 lpm, las *hazard ratio* del evento principal fueron, respectivamente, 2,233 (intervalo de confianza del 95%, 1,250-3,989, $p = 0,007$) y 0,380 (intervalo de confianza del 95%, 0,161-0,895; $p = 0,027$). Este

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parámetro presentó una tendencia decreciente en los primeros 10 años del trasplante (p = 0,001). Los pacientes con incremento neto de frecuencia cardiaca en el seguimiento mostraron mayor incidencia de eventos adversos.

Conclusiones: La frecuencia cardiaca elevada es un marcador pronóstico adverso tras el trasplante cardiaco.

Abbreviations

GVD: graft vascular disease
HF: heart failure
HRT: hear rate
HTx: heart transplantation

INTRODUCTION

An elevated heart rate (HRT) is an independent marker of cardiovascular risk.[1] Heart rate is strongly associated with the incidence of cardiovascular events in healthy individuals[2] and patients with hypertension,[3] coronary disease,[4] and heart failure (HF).[5] In addition, chronic treatment with heart rate-reducing agents, such as beta-blockers and ivabradine, improves prognosis in certain subgroups of patients with heart disease.[6–8]

Heart transplantation (HTx) continues to be the alternative therapy of choice in patients with refractory HF. For carefully selected candidates, HTx offers excellent long-term survival and quality of life.[9,10] As a result of autonomic denervation, HTx patients have a higher resting HRTthan individuals with native hearts.[11] Although this finding is often considered normal, some studies have indicated that HTx recipients with a higher heart rate may have worse survival.[12–14] In one of these studies,[14] the reduced survival was attributed to higher mortality from graft vascular disease (GVD). However, other authors[12] failed to see differences in the distribution of causes of death according to HRT values. Thus, the causal association between heart rate and GVD is controversial.[15–17]

The aim of the present study was to analyze the prognostic significance of HRT in HTx patients, particularly focusing on its association with survival, causes of death, and graft function, as well as to describe its long-term trend.

METHODS

Study Population

A retrospective analysis was conducted of a historical cohort of adult patients (> 18 years) who received an orthotopic HTx in our center between 1995 and 2005. The study included all patients who underwent surgery using a bicaval technique and who survived at least 1 year and were at that time in sinus rhythm. The following patients were excluded: those with repeat HTx, multiorgan transplantation, severe anemia (hemoglobin < 10 g/dL), a pacemaker, or treatment with beta-blockers, diltiazem, verapamil, digoxin, amiodarone, or ivabradine. The study protocol was approved by the *Comité Autonómico de Ética en la Investigación de Galicia*.

Protocol

Patients were treated according to the local protocol. All patients received induction therapy with muromonab-CD3 or basiliximab during the immediate postoperative period. The maintenance immunosuppressive regimen comprised various combinations of prednisone, calcineurin inhibitors (tacrolimus or cyclosporine), antiproliferative agents (mycophenolate mofetil or azathioprine), and mTOR inhibitors (everolimus or sirolimus).

Endomyocardial biopsies were systematically performed during the first post-HTx year and thereafter if there was suspicion of acute rejection. Antidonor antibodies and immunopathological markers of humoral rejection were also measured if there were suggestive clinical findings. Coronary angiography was initially performed only in patients suspected of having GVD. However, from 2003 onward, this procedure was also performed after 1 month and 1, 5, and 10 years after the HTx in asymptomatic patients, unless contraindicated.

Variables

Study data were retrospectively collected via medical history review. The resting HRT was determined from resting electrocardiograms performed in stable patients during regular visits to the outpatient service. Baseline HRT was determined at the end of the first post-HTx year and thereafter at annual intervals until the tenth post-HTx year. The baseline determination was calculated as the mean of all HRT measurements made via electrocardiograms obtained in outpatient visits between the tenth and twelfth month (fourth trimester) after the HTx. Updated information on the vital status of all study patients was obtained in March 2012. No patients were lost to follow-up.

The primary end point of the study was the composite outcome of all-cause mortality or graft dysfunction. Other events analyzed were the 2 individual components of the primary end point and cardiovascular mortality. Graft dysfunction was defined as any hospitalization due to clinical HF in the presence of a left ventricular ejection fraction (LVEF) < 45%, determined by echocardiography or ventriculography, or of restrictive graft physiology, determined by echocardiography or an invasive hemodynamic study.[18] Cardiovascular mortality was defined as that caused by HF, myocardial ischemia, or arrhythmia, including those deaths attributable to acute rejection, GVD, or any unexplained sudden death.

The causes of death were collected from autopsy reports and death certificates. Patients hospitalized due to graft dysfunction underwent a complete diagnostic work-up, including transthoracic echocardiography, coronary angiography, a hemodynamic study, and endomyocardial biopsy. A diagnosis of GVD was made in the presence of focal coronary stenosis > 50% in a main epicardial vessel or diffuse concentric thickening of the entire vessel. Acute cellular rejection was considered the cause of graft dysfunction if it was classified as histological grade 2R or higher.[19] In the absence of other causes, humoral rejection was considered to be the cause of graft dysfunction in patients who showed positive immunofluorescence for C4d with a pericapillary pattern.

Statistical Analysis

Categorical variables are presented as proportions, whereas continuous variables are presented as means (standard deviation). A Kolmogorov-Smirnov test was used to study the normality of the HRT values. Associations between baseline clinical characteristics and HRT were analyzed using Pearson's correlation coefficient for continuous variables, a Student *t* test for dichotomous qualitative variables, and analysis of variance with Bonferroni correction for qualitative variables with 3 or more categories.

Cox multivariate regression was used to determine the prognostic significance of the resting HRT at the end of the first post-HTx year. Based on clinical experience and the literature, the following candidate variables were selected for this analysis: donor age, recipient age, donor sex, recipient sex, diabetes mellitus, baseline heart disease and cytomegalovirus serological status, serum creatinine, and immunosuppression type. For each of the studied end points, a multivariate-adjusted model was constructed to include all variables whose entry or removal significantly changed the hazard ratio (HR) of the variable whose effect was the object of adjustment (HRT at the end of the first post-HTx year). Entry of the donor age was forced in all final models due to the correlation observed between this variable and heart rate. The variables retained in the final adjusted models were donor age, donor sex, and diabetes mellitus (death or graft dysfunction and all-cause mortality); donor age, donor sex, and recipient sex (cardiovascular mortality); and donor age (graft dysfunction).

For the analysis of follow-up events, patients were classified into 3 subgroups based on whether their HRT at the end of the first post-HTx year was found in the lower quartile, 2 middle quartiles, or upper quartile of the study population. Using the multivariate models described above, the adjusted HRs (aHRs) and cumulative incidence curves of the study events were calculated in these subgroups, considering as a reference category the patients with HRT in the 2 middle quartiles.

The HRT trend in the first 10 years after the HTx was studied using a repeated measures analysis of variance with Greenhouse-Geisser correction. In addition, the temporal trend in this parameter was estimated in each patient. The trend was considered increasing (a net increase in heart rate) in patients with a difference of > 0 between the mean of all annual HRT measurements and the baseline determination. Otherwise, the trend was considered decreasing (a net reduction in heart rate). The previously constructed multivariate models were used to calculate the aHRs and cumulative incidence curves of study events for the subgroups of patients with increasing and decreasing HRT trends during follow-up. $P < .05$ was considered significant for all comparisons. Statistical analysis was performed with SPSS 20.

RESULTS

Patients

Between 1995 and 2005, 393 patients received an orthotopic HTx in our center. Of these, 322 survived at least 1 year after the intervention. A total of 152 patients were excluded from this study for the following reasons: treatment with negative chronotropes (n = 132), simultaneous heart and renal transplantation (n = 4), repeat HTx (n = 2), severe anemia (n = 2), and absence of analyzable electrocardiograms (n = 12). The study population consisted of the 170 remaining patients. Their baseline clinical characteristics are shown in Table 1.

At the end of the first post-HTx year, the resting HRT of the study population had a normal distribution (Kolmogorov-Smirnov test, $P = .522$). The mean HRT was 96.1 (SD, 1.4) bpm, and the first, second, third, and fourth quartiles were 55-89, 90-96, 97-104, and 105-132 bpm, respectively. The only baseline clinical variable showing a statistically significant correlation with HRT at the end of the first post-HTx year was donor age ($r = –0.253$; $P = .001$). The correlations between the different baseline clinical variables studied and HRT are shown in Tables 1 and 2 of the Supplementary Material.

Table 1
Clinical Characteristics of the Patients Included in the Study

Recipients	
Age, mean (SD), y	52.9 (12.6)
Women	34 (20)
Baseline heart disease	
Ischemia	56 (32.9)
Dilated	84 (49.4)
Other	30 (17.6)
Diabetes mellitus	36 (21.2)
Hypertension	111 (65.3)
Creatinine, mean (SD), mg/dL	1.44 (0.49)
Body mass index, mean (SD)	25.6 (5.4)
Donors	
Age, mean (SD), y	39.6 (13.3)
Women	42 (24.7)
Cytomegalovirus serology	
Recipient +	144 (84.7)
Recipient –/donor +	20 (11.8)
Recipient –/donor –	6 (3.5)
Transplantation surgery	
Urgent transplantation	34 (20)
Ischemia time, mean (SD), min	182.1 (81.1)
CPB time, mean (SD), min	119.6 (30.6)
Immunosuppression	
Muromonab-CD3	86 (50.6)
Basiliximab	84 (49.4)
Cyclosporin	153 (90)
Tacrolimus	16 (9.4)
Prednisone	170 (100)
Mycophenolate mofetil	134 (78.8)
Azathioprine	30 (17.6)
Sirolimus or everolimus	7 (4.1)

CPB, cardiopulmonary bypass; SD, standard deviation.
Unless otherwise indicated, values are expressed as No. (%).

Adverse Events

During a mean follow-up of 8.9 (SD, 3.1) years, 20 patients (11.8%) had graft dysfunction and 47 (27.6%) died. The composite primary study end point occurred in 55 patients (32.3%). Graft dysfunction was attributed to GVD in 10 patients, to humoral rejection in 4, and cellular rejection in 3. No specific cause of the graft dysfunction could be identified in the 3 remaining patients.

In addition, 23 deaths (48.9%) were attributed to cardiac causes: refractory HF in 7 patients (secondary to GVD in 5 patients and to cellular rejection in 2 patients) and sudden death in 16 patients (5 of these had a previous diagnosis of GVD). Noncardiovascular mortality was due to neoplasms (n = 13), infection (n = 8), liver disease (n = 1), drug abuse (n = 1), and hemorrhage (n = 1).

Prognostic Value of Heart Rate

The univariate Cox analysis showed a statistically significant association between a higher resting HRT at the end of the first post-HTx year and the incidence of the primary composite end point (crude HR = 1.042; 95% confidence interval [95%CI], 1.019-1.065; $P < .001$). This association continued to be significant (aHR = 1.054; 95%CI, 1.028-1.080; $P < .001$) following the multivariate adjustment (Table 2). In addition, a significant association was seen between HRT and the risk of all-cause mortality (aHR = 1.058; 95%CI, 1.030-1.087; $P = .001$), as well as the risk of cardiovascular mortality (aHR = 1.069; 95%CI, 1.026-1.113; $P < .001$). There was no statistically significant association between HRT and the risk of graft dysfunction (aHR = 1.028; 95%CI, 0.989-1.069; $P = .161$).

The cumulative incidence curves of each of the study end points in the subgroups of patients with HRT in the lower quartile (< 90 bpm), in the 2 middle quartiles (90-104 bpm), and in the upper quartile (≥ 105 bpm) are shown in Figure 1. Compared with the middle reference category, the aHRs for the main composite end point were 2.233 (95%CI, 1.250-3.989; $P = .007$) and 0.380 (95CI%, 0.161-0.895; $P = .027$) in patients with heart rates ≥ 105 and < 90 bpm, respectively. The aHRs for the other study end points are shown in Table 3.

Long-term Heart Rate Changes

During the first 10 years of follow-up after the HTx, the mean HRT of the study population showed a linear decreasing trend ($P = .001$) (Figure 2). Patients showing a net increase in HRT during follow-up had a significantly higher incidence of the primary composite end point (aHR = 2.857; 95%CI, 1.514-5.391; $P = .001$) than patients with a net decrease in heart rate. The risks of all-cause mortality (aHR = 2.104; 95%CI, 1.069-4.142; $P = .031$), graft dysfunction (aHR = 6.839; 95%CI, 2.371-19.730; $P < .001$), and cardiovascular mortality (aHR = 4.051; 95%CI, 1.536-10.684; $P = .005$) were also significantly higher in patients with a net increase in heart rate. The cumulative incidence curves of end points based on the change in the HRT over time are shown in Figure 3.

DISCUSSION

The present study supports the prognostic value of HRT in HTx patients. In our series, the presence of a higher resting HRT at the end of the first post-HTx year was independently associated with an increased cumulative incidence of the composite end point of all-cause mortality and graft dysfunction. This result was due to increased overall mortality; however, the tendency toward a higher risk of graft dysfunction failed to reach statistical significance, probably due to the small number of events and the low statistical power for the individual analysis of these events. Notably, the prognostic significance of HRT was not limited to a single measurement, because the temporal tendency of the parameter was shown to be a prognostic marker independently of the baseline values.

Heart transplant operations necessitate transection of the autonomic fibers innervating the native heart. Due to the lack of parasympathetic stimulation, the HRT of transplanted hearts are largely determined by their response to circulating catecholamines.[11] Compared with healthy controls, HTx recipients show a persistent elevation of resting HRT with limited circadian variability and a delayed response to exercise.[11] A "normal" HRT remains to be clearly defined, with mean values in different series varying between 85 and 100 bpm.[12–17] This apparent variability is due to differences in surgical techniques, donor age, and drug treatment, as well as the time since the HTx, because some patients experience a gradual reinnervation phenomenon of the graft that progressively reduces the heart rate.[20]

At the end of the first post-HTx year, the resting HRT values in our population were normally distributed, with mean and median coinciding at 96 bpm and a middle interquartile range of 90 to 104 bpm. In relation with this reference category, patients with a HRT ≥ 105 bpm showed an increase of more than twice the incidence of the primary end point of death or graft dysfunction, whereas this incidence was reduced to a similar extent in those patients with a HRT < 90 bpm. Similarly, Anand et al[12] and Castel et al[14] observed significantly lower survival in HTx patients with a resting HRT > 90 bpm than in those with a HRT < 90 bpm, whereas Melero-Ferrer et al[13] reached a similar conclusion using a 100 bpm threshold. Measurement of HRT was performed at

Table 2
Clinical Variables Associated with the Primary Composite End Point of Death or Graft Dysfunction: Multivariate Cox Proportional Hazards Analysis

	HR (95%CI)	*P*	aHR (95%CI)	*P*
Heart rate	1.042 (1.019-1.065)	<.001	1.054 (1.028-1.080)	<.001
Recipient age	1.017 (0.994-1.042)	.149		
Recipient sex	0.660 (0.312-1.399)	.278		
Ischemic heart disease	1.305 (0.999-1.704)	.051		
Diabetes mellitus	1.543 (0.862-2.765)	.145	1.670 (0.925-3.014)	.089
Hypertension	0.794 (0.425-1.480)	.467		
Creatinine	1.118 (0.643-1.946)	.692		
Body mass index	1.021 (0.984-1.060)	.274		
Donor age	1.001 (0.990-1.029)	.365	1.028 (1.006-1.050)	.011
Female donor	0.477 (0.233-0.978)	.043	0.486 (0.235-1.008)	.053
Ischemia time	1.003 (1-1.007)	.049		
CPB time	1.009 (1.001-1.017)	.030		
Urgent heart transplantation	1.229 (0.600-2.515)	.573		
CMV D -/R + serology	1.307 (0.520-3.284)	.569		
Tacrolimus use	0.929 (0.334-2.580)	.887		
Mycophenolate mofetil use	0.832 (0.453-1.526)	.552		

95%CI, 95% confidence interval; aHR, adjusted hazard ratio; CMV, cytomegalovirus; CPB, cardiopulmonary bypass; D, donor; HR, crude hazard ratio; R, recipient.

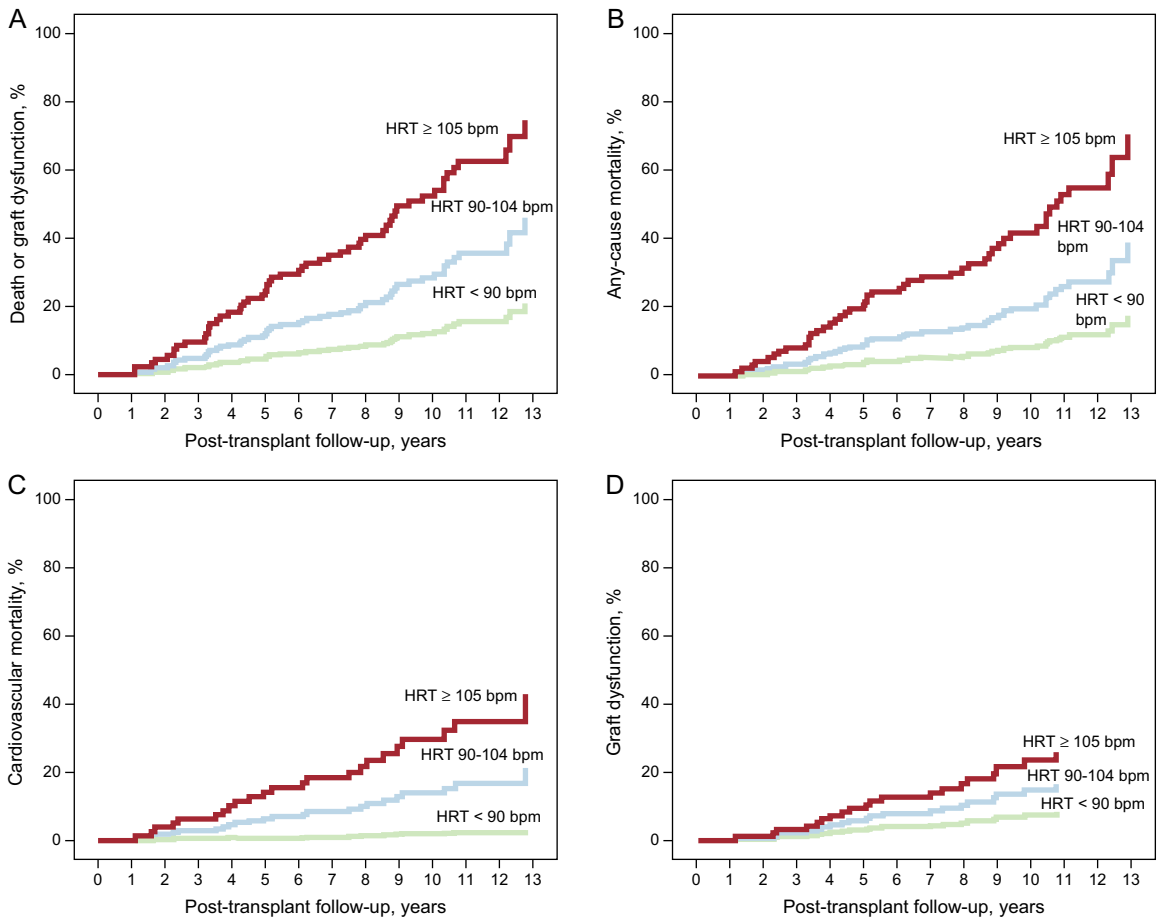

Figure 1. Cox multivariate analysis: cumulative incidence curves of end points in 3 resting heart rate categories. Bpm, beats per minute; HRT, heart rate.

1 post-HTx year in 2 of these studies[13,14] and at 3 months in the other.[12]

The negative prognostic impact of the elevated HRT values seen in our study is attributable to an increased risk of cardiovascular mortality, mainly refractory HF and sudden death. The most frequent underlying heart disease in these patients was GVD, which was the cause of death in close to half of the patients who died of cardiac causes. However, the absence of systematic coronary angiographies in patients who received transplants during the first years of the study hinders a more accurate estimation of the impact of GVD on cause of death in our

Table 3
Multivariate Cox Proportional Hazards Analysis

	aHR (95%CI)	*P*
Death or graft dysfunction		
HRT ≥ 105 bpm	2.233 (1.250-3.989)	.007
HRT < 90 bpm	0.380 (0.161-0.895)	.027
All-cause mortality		
HRT ≥ 105 bpm	2.476 (1.324-4.630)	.005
HRT < 90 bpm	0.392 (0.153-1.004)	.051
Graft dysfunction		
HRT ≥ 105 bpm	1.677 (0.628-4.477)	.302
HRT < 90 bpm	0.472 (0.128-1.739)	.259
Cardiovascular mortality		
HRT ≥ 105 bpm	2.407 (1-5.798)	.050
HRT < 90 bpm	0.120 (0.015-0.937)	.043

95%CI, 95% confidence interval; aHR, adjusted hazard ratio; bpm, beats per minute; HRT, heart rate.
aHRs of the study end points in 3 resting heart rate categories at the end of the first post-transplant year. Risk estimation was performed with respect to the reference category of patients with a heart rate within the 2 middle quartiles (90-104 bpm).

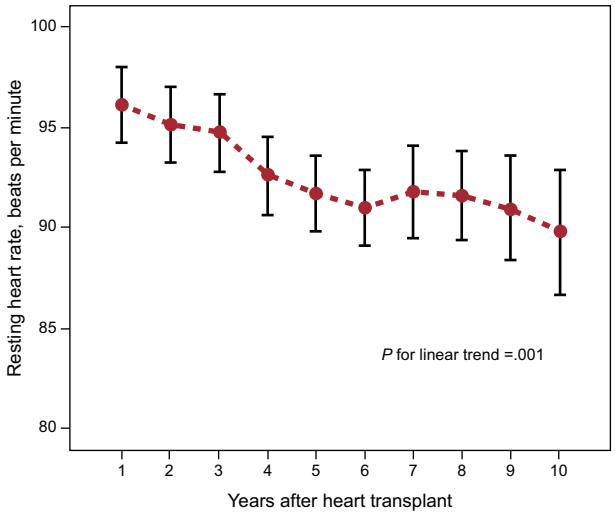

Figure 2. Temporal trend in the resting heart rate in the first 10 years after transplantation. The points represent mean heart rate values of the end of the first year and in the subsequent annual follow-ups, and the error bars indicate the respective 95% confidence intervals.

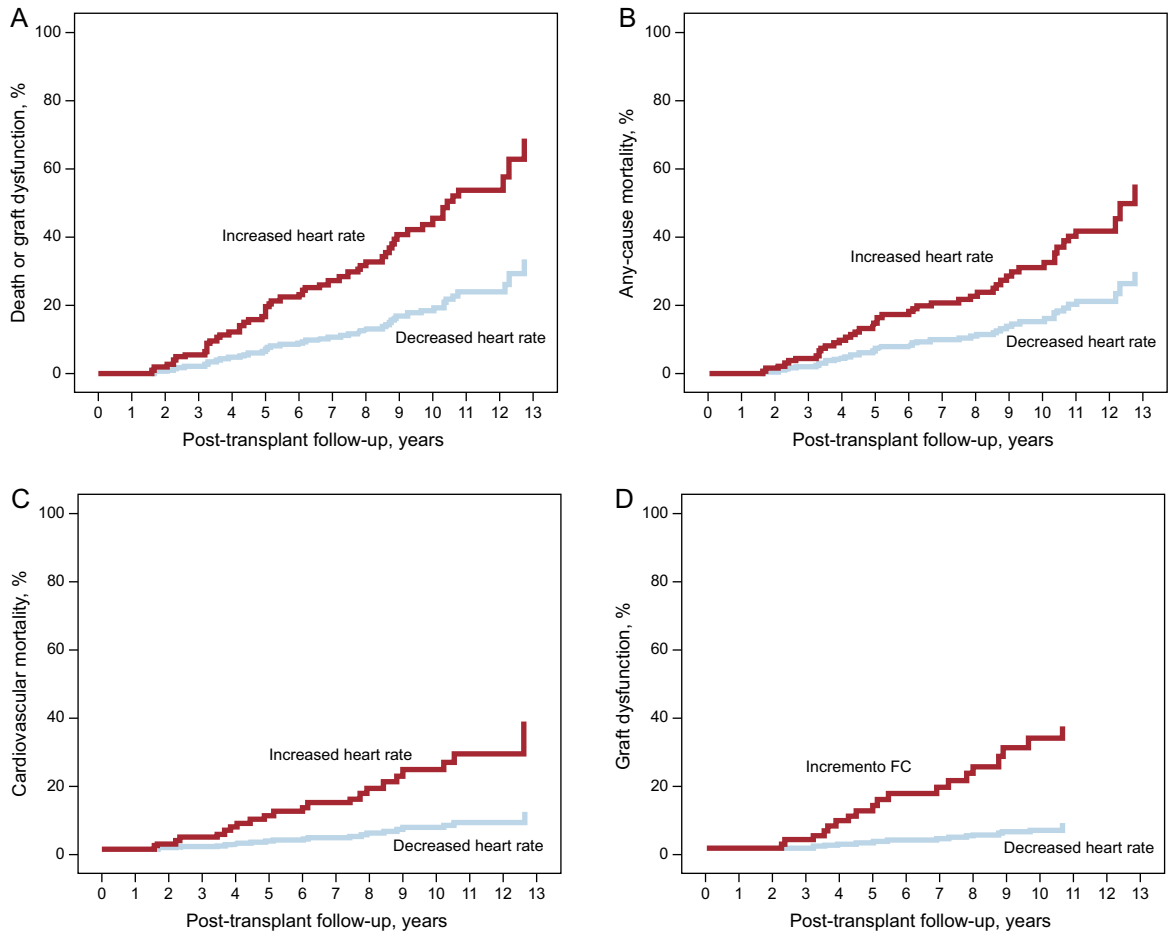

Figure 3. Multivariate Cox proportional hazards analysis: cumulative incidence curves of end points in patients who experienced a net increase or net reduction in heart rate during follow-up.

population. In fact, the rate of GVD was likely higher than that detected, given the high proportion of unexplained sudden deaths. In the study by Castel et al,[14] the lower survival of HTx recipients with higher HRT values was attributed to an increased mortality from GVD. However, Anand et al[12] failed to see any association between resting HRT and the distribution of the causes of death. No specific information on causes of mortality was provided in the study of Melero-Ferrer et al.[13]

The reasons for the association between HRT and risk of death remain to be determined in HTx patients. In some cases, the high HRT can be attributed to an adaptive reaction[21] to an underlying adverse clinical condition such as hypovolemia, anemia, graft dysfunction, bronchopulmonary disease, infection, or neoplasia, so that it should be interpreted as a risk marker rather than a strict risk factor. Nevertheless, permanent tachycardia could by itself play a causal role in the development of contractile dysfunction of the graft, mediated by myocardial energy depletion.[21] In other cases, the HRT elevation can reflect a high concentration of circulating catecholamines, which increase the risk of hypertension, myocardial ischemia, adverse ventricular remodeling, and arrhythmogenesis.[22] In addition, it must be remembered that persistent HRT elevation in patients with a native heart is implicated in the genesis and progression of coronary artery disease.[23] High HRT stimulates the endothelial expression of adhesion molecules and cytokines such as interleukin-6 and tumor necrosis factor-alpha,[24] which can hypothetically promote an immunological response against the coronary vessels of the graft. Nevertheless, studies have yet to show a clear association between a persistently high HRT and increased risk of GVD in HTx recipients.[15–17]

The natural history of HTx patients includes a gradual reinnervation of the graft with a progressively reduced resting HRT and improved response of HRT to exercise.[20,21] The mean HRT in our population gradually fell in the first 10 years after HTx. Notably, the incidence of the primary composite end point was significantly higher in patients with a net increase in HRT in this period than in those who experienced the expected net decrease. Anand et al[12] described a similar association between a decreasing trend in the resting HRT and a lower long-term rate of mortality. The progressive HRT decrease after HTx likely reflects the recovery of effective parasympathetic innervation of the graft. This phenomenon counteracts the deleterious effects of chronic adrenergic stimulation and is thus considered important for long-term maintenance of the contractile function of the transplanted heart.[21,25] Nonetheless, parasympathetic reinnervation of the graft is less frequent than sympathetic reinnervation.[26,27]

Prognostic benefit has been seen in HF and coronary disease patients chronically treated with heart rate-reducing drugs, such as beta-blockers and ivabradine.[8–10] However, their efficacy in HTx recipients remains unknown. In general, treatment of these patients with beta-blockers is discouraged, because these agents can worsen the contractile function of the graft and exercise capacity.[28,29] A preliminary study indicated that diltiazem use

during the first post-HTx year could slow the progression of GVD,[30] but this benefit was not subsequently confirmed. Recently, a small study showed that ivabradine is a safe drug, well tolerated and effective for reducing HRT in HTx patients in sinus rhythm,[31] but there are still no conclusive data on its potential clinical benefit in this population.

The present study has some limitations. Due to its observational and retrospective design, the study could be affected by selection and information biases inherent to this type of research. In addition, despite the use of rigorous multivariate adjustment, we are unable to rule out a possible effect of another untested confounding factor on the observed association between HRT and adverse events. The absence of information on the onset of de novo tachyarrhythmias during follow-up is another limitation, even if it is unlikely to significantly impact the observed results because of its low incidence in patients undergoing surgery using the bicaval technique.[32] Finally, the limited context of this single-center study indicates that its external relevance cannot be guaranteed and that the findings should be confirmed in larger multicenter populations.

Compared with previous studies examining the relationship between HRT and prognosis following HTx (all single center and with small sample sizes),[12–14] the main strengths of this work are its long follow-up, the rigorous selection criteria (eg, use of the same surgical technique in all patients, exclusion of patients with drugs or comorbidity that could affect heart rate), the analysis of other end points besides total mortality (eg, graft dysfunction, cardiovascular mortality), and the description of the temporal trend in HRT and its prognostic implication.

CONCLUSIONS

The present study confirms the existence of a strong association between higher resting HRT values and worse long-term prognosis in HTx patients. This association is largely due to an increased risk of cardiovascular mortality, mainly GVD, through sudden death and refractory HF. According to our results, the prognosis is particularly adverse for patients with a markedly higher resting HRT ($>$ 105 bpm) at the end of the first post-HTx year and those whose HRT tended to increase over time. This study supports the introduction of resting HRT as a simple and easily measured marker of risk in the clinical management of HTx patients and indicates the need for new studies evaluating the potential clinical benefit of heart rate-reducing drugs in this population. The confirmation of the favorable long-term prognosis shown by HTx patients with a resting HRT $<$ 90 bpm, in line with that observed in previous studies, supports this cutoff value as a hypothetical therapeutic target in future intervention studies.

CONFLICTS OF INTEREST

None.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found in the online version available at doi:10.1016/j.rec.2014.09.028.

REFERENCES

1. Kannel WB, Kannel C, Paffenbarger RS, Cupples LA. Heart rate and cardiovascular mortality: The Framingham study. Am Heart J. 1987;113:1489–94.
2. Cooney MT, Vartiainen E, Laatikainen T, Juolevi A, Dudina A, Graham IM. Elevated resting heart rate is an independent risk factor for cardiovascular disease in healthy men and women. Am Heart J. 2010;159:612–9.
3. Palatini P, Thijs L, Staessen JA, Fagard RH, Bulpitt CJ, Clement DL, et al. Predictive value of clinic and ambulatory heart rate for mortality in elderly subjects with systolic hypertension. Arch Intern Med. 2002;162:2313–21.
4. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (beautiful): A subgroup analysis of a randomised controlled trial. Lancet. 2008;372:817–21.
5. Bohm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, et al. Heart rate as a risk factor in chronic heart failure (SHIFT): The association between heart rate and outcomes in a randomised placebo-controlled trial. Lancet. 2010;376:886–94.
6. McAlister FA, Wiebe N, Ezekowitz JA, Leung AA, Armstrong PW. Meta-analysis: beta-blocker dose, heart rate reduction, and death in patients with heart failure. Ann Intern Med. 2009;150:784–94.
7. Fox K, Ford I, Steg PG, Tendera M, Ferrari R. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (beautiful): A randomised, double-blind, placebo-controlled trial. Lancet. 2008;372:807–16.
8. Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): A randomised placebo-controlled study. Lancet. 2010;376:875–85.
9. González-Vílchez F, Gómez-Bueno M, Almenar L, Crespo-Leiro MG, Arizón JM, Martínez-Sellés M, et al. Registro Español de Trasplante Cardiaco. XXIV Informe Oficial de la Sección de Insuficiencia Cardiaca y Trasplante Cardiaco de la Sociedad Española de Cardiología (1984-2012). Rev Esp Cardiol. 2013;66:973–82.
10. Jaramillo N, Segovia J, Gómez-Bueno M, García-Cosío D, Castedo E, Serrano S, et al. Características de los pacientes con supervivencia mayor de 20 años tras un trasplante cardiaco. Rev Esp Cardiol. 2013;66:797–802.
11. Stecker EC, Strelich KR, Chugh SS, Crispell K, McAnulty JH. Arrhythmias after orthotopic heart transplantation. J Cardiac Fail. 2005;11:464–72.
12. Anand RG, Reddy MT, Yau CL, Myers L, Amin RR, Stahls PF, et al. Usefulness of heart rate as an independent predictor for survival after heart transplantation. Am J Cardiol. 2009;103:1290–4.
13. Melero-Ferrer JL, Sanchez-Lazaro IJ, Almenar-Bonet L, Martinez-Dolz L, Buendia-Fuentes F, Portoles-Sanz M, et al. Impact of basal heart rate on long-term prognosis of heart transplant patients. Transplant Intern. 2013;26:502–7.
14. Castel MA, Roig E, Rios J, Tomas C, Mirabet S, Cardona M, et al. Long-term prognostic value of elevated heart rate one year after heart transplantation. Int J Cardiol. 2013;168:2003–7.
15. Ambrosi P, Kreitmann B, Habib G. Does heart rate predict allograft vasculopathy in heart transplant recipients? Int J Cardiol. 2010;145:256–7.
16. Olmetti F, Pinna GD, Maestri R, D'Armini A, Pellegrini C, Vigano M, et al. Heart rate and cardiac allograft vasculopathy in heart transplant recipients. J Heart Lung Transplant. 2011;30:1368–73.
17. Gullestad L, Ross H, Myers J, Hoang K, Hunt S, Stinson EB, et al. Importance of decreased heart rate in predicting transplant coronary artery disease. Clin Transplant. 1997;11:628–32.
18. Mehra MR, Crespo-Leiro MG, Dipchand A, Ensminger SM, Hiemann NE, Kobashigawa JA, et al. International Society for Heart and Lung Transplantation working formulation of a standardized nomenclature for cardiac allograft vasculopathy-2010. J Heart Lung Transplant. 2010;29:717–27.
19. Stewart S, Winters GL, Fishbein MC, Tazelaar HD, Kobashigawa J, Abrams J, et al. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. J Heart Lung Transplant. 2005;24:1710–20.
20. Wilson RF, Johnson TH, Haidet GC, Kubo SH, Mianuelli M. Sympathetic reinnervation of the sinus node and exercise hemodynamics after cardiac transplantation. Circulation. 2000;101:2727–33.
21. Katz AM. The myocardium in congestive heart failure. Am J Cardiol. 1989;63:A12–6.
22. Sekar B, Critchley WR, Williams SG, Shaw SM. Should we consider heart rate reduction in cardiac transplant recipients? Clin Cardiol. 2013;36:68–73.
23. Fox K, Borer JS, Camm AJ, Danchin N, Ferrari R, Lopez Sendon JL, et al. Resting heart rate in cardiovascular disease. J Am Coll Cardiol. 2007;50:823–30.
24. Walpola PL, Gotlieb AI, Cybulsky MI, Langille BL. Expression of ICAM-1 and VCAM-1 and monocyte adherence in arteries exposed to altered shear stress. Arterioscler Thromb Vasc Biol. 1995;15:2–10.
25. De Jong MJ, Randall DC. Heart rate variability analysis in the assessment of autonomic function in heart failure. J Cardiovasc Nurs. 2005;20:186–95.
26. Bengel FM, Ueberfuhr P, Schiepel N, Nekolla SG, Reichart B, Schwaiger M. Effect of sympathetic reinnervation on cardiac performance after heart transplantation. N Engl J Med. 2001;345:731–8.
27. Arrowood JA, Minisi AJ, Goudreau E, Davis AB, King AL. Absence of parasympathetic control of heart rate after human orthotopic cardiac transplantation. Circulation. 1997;96:3492–8.
28. Bexton RS, Milne JR, Cory-Pearce R, English TA, Camm AJ. Effect of beta blockade on exercise response after cardiac transplantation. Br Heart J. 1983;49:584–8.
29. Verani MS, Nishimura S, Mahmarian JJ, Hays JT, Young JB. Cardiac function after orthotopic heart transplantation: Response to postural changes, exercise, and beta-adrenergic blockade. J Heart Lung Transplant. 1994;13:181–93.

30. Schroeder JS, Gao SZ, Alderman EL, Hunt SA, Johnstone I, Boothroyd DB, et al. A preliminary study of diltiazem in the prevention of coronary artery disease in heart transplant recipients. N Engl J Med. 1993;328:164–70.
31. Doesch AO, Celik S, Ehlermann P, Frankenstein L, Zehelein J, Koch A, et al. Heart rate reduction after heart transplantation with beta-blocker versus the selective If channel antagonist ivabradine. Transplantation. 2007;84: 988–96.
32. Morgan J, Edwards N. Orthotopic cardiac transplantation: comparison of outcome using biatrial, bicaval, and total techniques. J Card Surg. 2005;20:. 102–6.