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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.