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Impact of basal heart rate on long-term prognosis of heart transplant patients

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Summary

Previous studies in patients with heart failure have shown that an elevated basal heart rate (HR) is associated with a poor outcome. Our aim with this study was to investigate if this relationship is also present in heart transplantation (HTx) recipients. From 2003 until 2010, 256 HTx performed in our center were recruited. Patients who required pacemaker, heart-lung transplants, pediatrics, re-transplants, and those patients with a survival of less than 1 year were excluded. The final number included in the analysis was 191. Using the HR obtained by EKG during elective admission at 1 year post-HTx and the survival rate, an ROC-curve was performed. The best point under the curve was achieved with 101 beats per minute (bpm), so patients were divided in two groups according to their HR. A comparison between survival curves of both groups was performed (Kaplan–Meier). Subsequently, a multivariate analysis considering HR and other variables with influence on survival according to the literature was carried out. A total of 136 patients were included in the group with HR $\leq$100 bpm, and 55 in the one with HR >100 bpm. There were no basal differences in both groups except for primary graft failure, which was more frequent in the >100 bpm group (30.9 vs. 17%, $P = 0.033$). Patients with $\leq$100 bpm had a better long prognosis ($P < 0.001$). The multivariate analysis proved that high HR was an independent predictor of mortality. Our study shows that HR should be considered as a prognosis factor in HTx patients.

Heart transplantation (HTx) is currently considered the most effective treatment for patients with advanced heart failure who have no other treatment options [1]. Advances in this field over the last decade have increased the average survival of recipients to more than 10 years [2]. However, morbidity and mortality rates of this population continue to be high. Thus, numerous studies have been conducted to identify risk markers that can be related to a worse prognosis in the clinical progress of these patients [3–7].

There are various epidemiological studies that have shown an inverse correlation between resting heart rate (HR) and life expectancy. This relationship has also been suggested both in healthy subjects [8,9] and in patients with cardiovascular diseases [10,11]. In fact, an increase in basal HR has been associated with higher mortality in patients with heart failure or stable coronary disease [12,13].

Owing to cardiac allograft denervation, HTx recipients have high HR [14] which decreases over time. This has been interpreted as a sympathetic reinnervation phenomenon. However, as this event does not occur in all the patients, it is theorized if, as occurs with other diseases, maintaining an elevated HR would be a marker of worse life expectancy.

Therefore, the aim of this study was to analyze whether the presence of higher HRs is related to higher medium- and long-term mortality rates in a population of heart transplant patients.

Materials and methods

A retrospective analysis was made involving all the HTx performed in our hospital from January 2003 to May 2010. Heart-lung transplants, pediatric transplants, retransplants, and patients requiring a pacemaker after HTx were excluded, as well as patients with a survival of less than 1 year. Of the 256 HTx recipients recruited, 191 were included in the final analysis after applying exclusion criteria.

This study was approved by the clinical research ethics committee of our hospital and was conducted in accordance with the Declaration of Helsinki. All participating patients signed the informed consent form.

Heart rate was measured during elective admission at 1 year post-HTx with a 12-lead EKG. Patients were in supine position and in basal state after resting at least 5 min according to our center's protocol. At the time of HR determination, none of the patients included in the study was taking drugs with any chronotropic effect (such as beta-blockers or ivabradine). Some of the patients were under antihypertensive treatment with renin-angiotensin-aldosterone axis inhibitors, nondihydropyridine calcium-antagonists or diuretics.

During that admission, besides standard laboratory analysis, echocardiography and endomyocardial biopsy were performed. In addition, in most patients (77%), coronary angiography with intravascular ultrasound (IVUS) of the left anterior descending artery was performed to assess intimal proliferation and, consequently, the development of cardiac allograft vasculopathy (CAV). We considered that CAV was present when we found at any point, an intimal proliferation >1 mm and/or >0.5 mm in 180° compared with the IVUS performed in this same population at the first month post-HTx.

An ROC curve was done using the HR and survival rates to decide which HR value at 1 year post-HTx offered the best area under the curve. The optimum cutoff point was 101 beats per minute (bpm) (sensitivity of 0.62 and specificity of 0.75). According to this value, patients were divided into two groups: Group 1: 136 patients with a HR $\leq$ 100 bpm, Group 2: 55 patients with a HR >100 bpm.

A comparison between survival curves of both groups was performed with the Log-rank test (Kaplan–Meier). Subsequently, a multivariate analysis was performed using Cox proportional hazards models, considering death as the dependent variable and, as independent variables, those that were significant in the univariate analysis and those with influence on survival according to the literature [primary graft failure (PGF), donor age, time of ischemia, number of rejection episodes and infections and renal dysfunction]. HR was included is this analysis as a quantitative variable rather than a dichotomic one. Owing to the lack of available data of CAV from all patients, we conducted the analysis twice, taking into account in the second Cox regression the presence of CAV. Moreover, a third multivariate analysis was completed to determine if any of the variables were associated with a higher HR at 1 year post-HTx.

As the definition of PGF is not standardized, our group considered PGF as severe ventricular dysfunction (EF <35%,) confirmed by echocardiography and/or clinical findings, or the need for high doses of vasoactive drugs (dobutamine >10 mcg/kg/min and/or noradrenaline) within the first 48 h after HTx. Rejection was considered when it was necessary to significantly increase immunosuppressive medication (grade 2R or higher biopsies and/or acute depression of ventricular function not because of CAV). Infection was considered if clinical symptoms required hospital admission or prolongation of hospital stay. Renal function was estimated by the Modification of Diet in Renal Disease (MDRD) equation.

Continuous variables are expressed as mean $\pm$ standard deviation. Student's *t*-test was used to compare independent groups. Qualitative variables were compared by the chi-square test. In both cases, a value of $P < 0.05$ was assumed to be statistically significant. Data were analyzed using the SPSS® version 9.0 statistical package (SPSS Inc., Chicago, IL, USA).

Results

Clinical characteristics

Clinical profiles of both groups are shown in Table 1. No differences were observed in terms of age or gender or in relevant parameters such as immunosuppression, graft function, number of infections, or number of rejection episodes during the first year. However, the presence of PGF was more frequent in the group with basal HR >100 bpm, and this difference was statistically significant (30.9% vs. 17%, $P = 0.033$). There were no differences between both groups on time up to first rejection.

Survival curves

When survival curves of both groups are compared (Fig. 1), it can be observed how there is a marked separation between both curves from the start, with differences becoming more pronounced as the follow-up period increases. This difference was significant with a log-rank test $P < 0.001$.

Multivariate analysis

The first multivariate analysis (Table 2) showed basal HR, donor age, and number of rejection episodes dur-

Table 1. Baseline patient characteristics.

	Basal HR ≤ 100	Basal HR >100	*P*
n	136	55	
Age at HTx (years)*	51 ± 12	54 ± 9	0.09
Male (%)	78.7	83.6	0.55
Donor age (years)	40 ± 11	35 ± 13	0.39
Ischemia time (min)	157 ± 49	165 ± 46	0.34
Cause of HTx			0.13
DCM (%)	41.9	25.5	
IHD (%)	40.4	50.9	
Others (%)	17.7	24.5	
AHT (%)	34.1	22.6	0.12
Diabetes (%)	19.8	29.1	0.17
Hypercholesterolemia (%)	40.4	50.9	0.19
Immunosuppression			
Cyclosporine (%)	78.9	69.1	0.16
Tacrolimus (%)	20.6	29.1	0.20
Primary graft failure (%)**	17	30.9	0.03
Admission for infection (not CMV)	0.89	0.96	0.43
CMV infection (%)	23.7	30.9	0.30
No. of rejections in first year	0.99	1.05	0.41
Cardiac allograft vasculopathy (%)	45.6	54.4	0.12
Creatinine at 1 year post-HTx	1.2 ± 0.4	1.3 ± 1.1	0.40
LVEF (%)	61.5	63.3	0.32
Proportion between BMI of recipient and donor (%)	100.63 ± 18.20	95.96 ± 19.65	0.13
Causes of death			
Cardiovascular (%)	53	47	0.55
Noncardiovascular (%)	42	58	

HTx, heart transplantation; DCM, dilated cardiomyopathy; IHD, ischemic heart disease; AHT, arterial hypertension; CMV, cytomegalovirus; LVEF, left ventricular ejection fraction; BMI, body mass index.
*$P < 0.1$; **$P < 0.05$.

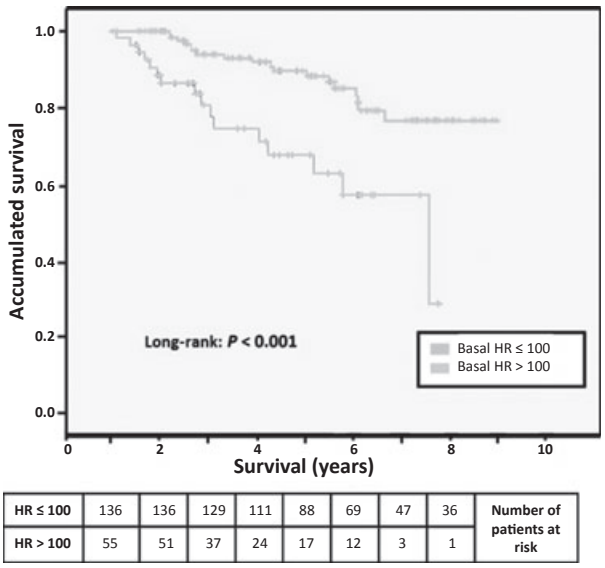

Figure 1 Survival according to basal HR.

Table 2. Multivariate analysis: long-term survival.

Covariables	*P*	HR	95% CI
Not including cardiac allograft vasculopathy			
Basal heart rate	0.007	2.12	1.04–4.23
Donor age	0.003	1.06	1.02–1.10
No. of rejections in first year	0.03	1.55	1.05–2.28
Ischemia time	0.56	1.01	0.99–1.02
Primary graft failure	0.21	1.68	0.74–3.82
No. of admissions because of infection in first year	0.13	0.73	0.48–1.10
Creatinine at 1 year post-HTx	0.67	0.92	0.65–1.32
Including cardiac allograft vasculopathy			
Basal heart rate	0.044	1.69	1.03–6.33
Cardiac allograft vasculopathy	0.039	2.85	1.05–7.72
Donor age	0.026	1.07	1.01–1.12
No. of rejections in first year	0.74	1.10	0.62–1.92
Ischemia time	0.36	1.01	0.99–1.02
Primary graft failure	0.34	1.72	0.56–5.30
No. of admissions because of infection in first year	0.60	1.18	0.63–2.18
Creatinine at 1 year post-HTx	0.36	0.80	0.50–1.28

Table 3. Multivariate analysis: heart rate determinants.

Dependent variable	Basal heart rate at 1 year		
Covariables	*P*	HR	95% CI
Cardiac allograft vasculopathy	0.75	0.32	−3.83–5.33
Donor age	0.68	−1.84	−0.37–0.01
Ischemia time	0.13	1.32	−0.01–0.07
Primary graft failure	0.38	−0.88	−7.50–2.86
No. of admissions because of infection in first year	0.31	1.01	−1.39–4.33
No. of rejections in first year	0.38	−0.89	−3.20–1.21

ing the first year as the only variables related to mortality during the follow-up. When we considered CAV into the analysis, this variable also achieve statistical signification, while number of rejection episodes loses its signification. PGF, time of ischemia, number of infections in the first year, and creatinine values (linear) remained not significant in both analyses. A high HR was an independent predictor variable of mortality. Thus, a HR higher than 100 bpm at 1 year post-HTx multiplies by between 1.7 and 2.1 the risk of dying in subsequent follow-up.

The second multivariate analysis (Table 3) was not able to demonstrate whether any of the analyzed variables were associated with basal HR >100 bpm at 1 year.

Discussion

It has been known for some years, that in patients with a native heart, both in healthy patients and in those with various cardiovascular diseases, elevated basal HRs have deleterious effects as they are invariably associated with decreased survival [8–11]. Recent studies have confirmed that an elevated HR is a risk factor for the development of adverse events, both in heart failure patients [13] and in those with stable ischemic heart disease [12]. Moreover, elevated HR has been postulated as risk factor for cardiovascular disease, playing a main role in the progression and severity of atherosclerotic lesions [14]. This makes HR an important therapeutic target, whose control and pharmacological reduction (beta-blockers, ivabradine) has proven to be related to an improved prognosis. Based on this, the study's goal was to clarify if there is an association between higher HR and mortality in stable HTx patients.

It has been widely studied and demonstrated that those patients receiving HTx show high basal HR values [15] and an abnormal response to exercise, mainly as a consequence of allograft denervation. Nevertheless, several studies have shown that, following transplantation, a considerable percentage of HTx patients recover chronotropic competence over time, as well as exercise capacity after some months [15, 16]. This is because of the occurrence of partial sympathetic reinnervation of the allograft. Another recent study has shown that this reinnervation is present in up to 40% of patients at 1 year post-HTx [17].

Although the relationships between HR and development of cardiovascular disease and between HR and prognosis have been widely studied in patients with a native heart, it was not clearly known if these associations would also be demonstrated in patients receiving an HTx.

A recent study performed by Olmetti *et al.* [18] assessed whether there was a relationship between HR and development of CAV in the HTx populations. However, elevated HR (>90 bpm) was not significantly associated with an increased CAV development, so the authors stated that higher HR was not a risk factor for coronary atherosclerosis. Surprisingly, a significant association was achieved between HR <90 bpm and CAV development. However, donor's age was significantly higher in the group with HR <90 bpm, biasing the real impact of HR over CAV.

A previous study [19] showed that ivabradine, like beta-blockers, was effective to reduce HR in transplant patients. However, its impact on mortality was not assessed. A further study of the same group exposed that selective reduction in HR with ivabradine in patients with symptomatic sinus tachycardia led to a significant reduction in left ventricle hypertrophy [20].

The study which has gone deepest into this topic was the one conducted by Anand *et al.* [21]. These authors included 78 patients during a 10-year follow-up and the HR was measured only 3 months post-HTx. These authors demonstrated that HTx patients with a HR >90 bpm post-HTx had an increased risk of death from any cause of 2.8 times greater than patients with a HR <90 bpm ($P = 0.004$). In addition, patients with a net increase in HR over time were 4.7 times more likely to die than those whose HR did not change or decreased.

In our study, we analyzed survival rates in HTx patients from our hospital by measuring (opposite to Anand *et al.*) basal HR at 1 year after surgery. At this time we consider that patients have reached a clinically stable status, and their immunosuppressive medication regimen is very similar to what they will be taking for the rest of their lives. On the other hand, when heart reinnervation occurs, this process is not complete until after the first year post-HTx [17]. So, in fact, we are analyzing survival conditional on 1-year survival, as seen in other studies [22].

Survival analysis was made using the Kaplan-Meier curve, taking as a cutoff point 100 bpm, as it was the value with the best area under the ROC curve. The survival curve showed a marked separation between both groups from the start of the observation period. This separation was more pronounced as time went by. Differences in cumulative survival between both groups were already of 13% at 500 days after HTx (100% vs. 87%), increasing to 18% at 1000 days (92% vs. 74%) and up to 23% at 2000 days after HTx (81% vs. 58%).

Although no significant differences were found in baseline characteristics of both groups, a statistically significant difference (30.9% vs. 17%, $P = 0.033$) was observed in the incidence of PGF in favor of the group with a HR higher than 100 bpm. This factor needs to be taken into account as PGF is per se a factor that has proven to reduce survival in HTx recipients. However, PGF has been associated with an increased early mortality in the immediate post-transplant period [23]. We therefore believe that the impact of this factor is not significant in long-term survival, since we took as the starting point for the study at 1 year after HTx.

Multivariate analysis shows that basal HR is an independent prognostic factor, as it maintains statistical significance. Among the factors included in the multivariate analysis with influence on survival according to the literature, only donor age and CAV offer a statistically significant result in both analyses. The number of rejection episodes also achieves statistical significance when CAV is not considered, but it loses its significance when the latter is included in the analysis. We think that the main reason to explain why all these well-known predictors of mortality described in larger studies did not predict mortality in this study is the fact that we are incurring a selection bias as we are only considering patients with a conditioned survival of at least 1 year.

An important question to consider is the fact that it could be possible that the higher HR observed in some

patients was because of an underlying more severe condition such as severe rejection or CAV which may lead in turn to a subsequent poor survival. In this picture, sinus tachycardia would be an epiphenomenon (a consequent compensatory mechanism) rather than a primary risk factor. Although both groups have similar baseline characteristics including rejection episodes or development of CAV, to reach a better explanation, a second multivariate analysis was performed. None of the analyzed variables (including rejection, donor age, and CAV) achieved signification in predicting HR >100 bpm at 1 year.

According to previous studies, HR reduction has several beneficial effects over cardiac function, which may explain why such reduction is related to an increased survival. In heart failure patients, elevated HRs has proven to be related to progressive mechanical desynchronization [24]. Conversely, lower HRs implies more prolonged diastoles and therefore a better myocardial perfusion [25]. In addition, HR reduction causes a decrease in cardiac muscle's energy consumption [26], which is partly mediated by ventricular afterload reduction that is directly related to HR [27].

This study has several limitations. Relatively limited sample size was a limitation. Its design as a retrospective analysis was another. On one hand, it takes as reference HR measures at a specific time in the patient's progress. On the other, coronary angiography with IVUS was not performed in all patients. Moreover, as we assessed survival conditional on 1 year survival, a selection bias is incurred. However, this is the first study in the literature that analyzes and documents the independent prognostic value of HR in HTx patients.

In conclusion, data obtained in our study show that basal HR at 1 year post-HTx in stable HTx patients may help to identify a subgroup at risk of worse clinical outcome. This would force us to design closer clinical care strategies for these patients and to consider the administration of HR lowering drugs. The impact on survival of HR reduction with drugs will define future lines of research in HTx.

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