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Is Heart Rate Important for Patients With Heart Failure in Atrial Fibrillation?

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Objectives This study sought to investigate the relationship between resting ventricular rate and mortality in patients with chronic heart failure (CHF) and reduced left ventricular ejection fraction (LVEF) who were in sinus rhythm (SR) or atrial fibrillation (AF).

Background Slower heart rates are associated with better survival in patients with CHF in SR, but it is not clear whether this is true for those in AF.

Methods We assessed 2,039 outpatients with CHF and LVEF ≤50% undergoing baseline assessment, of whom 24% (n = 488) were in AF; and 841 outpatients reassessed after attempted treatment optimization at 1 year, of whom 22% (n = 184) were in AF. Cox proportional hazards models were used to assess the relationships between heart rate and survival in patients with CHF and AF or sinus rhythm. We analyzed heart rate and rhythm data recorded at the baseline review and after 1-year follow-up. Proportional hazards assumptions were checked by Schoenfeld and Martingale residuals.

Results The median survival for those in AF was 6.1 years (interquartile range [IQR]: 5.3 to 6.9 years) and 7.3 years (IQR: 6.5 to 8.1 years) for those in SR. In univariable analysis, patients with AF had a worse survival (hazard ratio [HR]: 1.26, 95% confidence interval [CI]: 1.08 to 1.47; p = 0.003) but after covariate adjustment, survival rates were similar. After adjusting Cox regression models, there was no association between heart rate (per 10 beats/min increments) and survival in patients with AF before (HR: 0.94, 95% CI: 0.88 to 1.00, p = 0.07) or after (HR: 1.00, 95% CI: 0.99 to 1.00, p = 0.84) therapy optimization. For patients in SR, higher heart rates were associated with worse survival, both before (HR: 1.10, 95% CI: 1.05 to 1.15, p <0.0001) and after (HR: 1.13, 95% CI: 1.03 to 1.24, p = 0.008) therapy optimization.

Conclusions In patients with CHF and a reduced LVEF, slower resting ventricular rate is associated with better survival for patients in SR but not for those with AF. (J Am Coll Cardiol HF 2014;2:213–20) © 2014 by the American College of Cardiology Foundation

Resting heart rate is a powerful prognostic marker in a broad range of subjects in sinus rhythm (SR), with or without cardiovascular disease (1–3). In patients with chronic heart failure (CHF) in SR due to left ventricular systolic dysfunction (LVSD), a lower resting heart rate is associated with better survival and fewer hospital readmissions due to heart failure (4,5). In contrast, a lower resting ventricular rate (<80 beats/min) is not associated with better survival in patients with permanent atrial fibrillation (AF), although studies have included few patients with CHF (6–8). Furthermore, there is little evidence that lower resting ventricular rate in patients with CHF and AF is important physiologically or improves quality of life (9–11). Accordingly, we investigated the relationship between ventricular rate and survival in patients with CHF due to LVSD who were in AF or SR.

Methods

Study population and data collection. We included outpatients with CHF who attended a community-based heart failure program in Kingston-Upon-Hull, United Kingdom, serving a population of 600,000 people, between September 1999 and October 2010. Patients were referred for diagnosis and/or management of CHF. Patients gave written consent for their data to be stored electronically and used for research purposes. A large proportion of surviving patients were reassessed at 1 year after attempts had

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Abbreviations and Acronyms

ACE-I = angiotensin-converting enzyme inhibitor
AF = atrial fibrillation
ARB = angiotensin receptor blocker
CHF = chronic heart failure
DBP = diastolic blood pressure
HR = heart rate
IHD = ischemic heart disease
IQR = interquartile range
LBBB = left bundle branch block
LVSD = left ventricular systolic dysfunction
NYHA = New York Heart Association
SBP = systolic blood pressure
SR = sinus rhythm

been made to optimize therapy in accordance with UK guidelines for the management of chronic heart failure (12).

All patients underwent a standardized clinical examination, 12-lead electrocardiography, echocardiography, spirometry, and routine blood tests. Cardiac rhythm and resting heart rate were determined from a 12-lead electrocardiogram, which was obtained after at least 5 min rest in the supine position, using a MAC 5000 machine (GE Healthcare, Milwaukee, Wisconsin). We used the arbitrary definitions of the RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient versus Strict Rate Control II) study to categorize patients in AF into those with "lenient" (≥80 and <110 per min) or "strict" (<80 per min) ventricular rate control (7). Patients who were permanently paced were excluded from the analysis.

All echocardiograms were performed by experienced echocardiographers in accordance with recommendations of the British Society of Echocardiography. For echocardiogram acquisition, a Vivid 5 or Vivid 7 system (GE Healthcare) using a 3.4-MHz probe was used. When possible, the Simpson's biplane method was used to measure the left ventricular ejection fraction (LVEF), and, in all cases, a visual approximation was made. Only patients with at least mild left ventricular systolic dysfunction (LVSD) were included.

The primary endpoint of the study was all-cause mortality. Mortality data were captured electronically by National Health Service information systems and reported to the hospital and were complete to the censor date of August 31, 2011.

Ethics. The investigation conformed to the principles outlined in the Declaration of Helsinki. It was approved by the Hull and East Yorkshire Research Ethics Committee (Heart Care Study ELSY 2642). All subjects gave written informed consent.

Statistical methods. Data were tested for normality using the Kolmogorov-Smirnov test. Normally distributed data are presented as mean ± SD; other data are presented as medians and interquartile ranges (IQR). Categorical data are given as percents. Differences in categorical variables between groups were compared with the chi-square test. Differences between groups with normally distributed data were analyzed using Student's *t* test, and non-normally distributed data were analyzed using the Mann-Whitney *U* test.

Kaplan-Meier curves used for analysis of survival and significance tests between groups were tested using the log-rank test. Univariate and multivariate Cox regression models were constructed to investigate the relationship between potential covariates and outcome. To avoid overfitting, we included only variables significantly associated with outcome in the univariate analysis ($p < 0.05$) in the forward conditional stepwise Cox analysis. Proportional hazards assumptions were checked by Schoenfeld residuals, and Martingale residuals plots were used to evaluate linearity (13,14). Results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Analyses were performed using SPSS version 19 (IBM Corp., Armonk, New York) and Stata 13 software (StataCorp., College Station, Texas).

Results

Baseline patient characteristics. A total of 2,039 patients was included in the baseline analysis, of whom 24% (n = 488) had AF (Table 1). Compared to patients in SR, patients in AF were older and less likely to be diabetic or to have ischemic heart disease. Although there were no differences in severity of LVSD, patients with AF were more symptomatic than patients in SR. Patients with AF were less likely to be prescribed a beta-blocker, aldosterone antagonist, statin, or aspirin but more likely to be prescribed warfarin, digoxin, or a loop diuretic agent. The median resting heart rate was higher for patients with AF than for patients with SR (81 per min [IQR: 69 to 98 per min] versus 70 per min (IQR: 60 to 83 per min), respectively, p = 0.0001).

Relationship between heart rhythm and survival. During the follow-up period, 229 patients (47%) with AF died compared to 639 patients (41%) with SR. The 1-year mortality rate for patients with AF was 15% (n = 74) versus 11% for patients with SR (n = 170). Overall median follow-up was 3.6 years (IQR: 1.7 to 6.9 years). The overall median survival for patients with AF was 6.1 years (IQR: 5.3 to 6.9 years) compared to 7.3 years (IQR: 6.5 to 8.1 years) for patients with SR.

In a multivariable model using baseline data that was corrected for age, sex, weight, QRS duration, heart rate, systolic blood pressure, New York Heart Association (NYHA) functional class III/IV versus I/II, ischemic heart disease (IHD) status (yes/no), diabetic status (yes/no), angiotensin-converting enzyme/angiotensin receptor blocker (ACE/ARB) use (yes/no), LVSD severity (≥moderate vs. <moderate), loop diuretic agent use (yes/no), aldosterone antagonist use (yes/no), beta-blocker use (yes/no), digoxin use (yes/no), and amiodarone use (yes/no), survival rates among patients with AF or SR were no different (HR: 0.94; 95% CI: 0.77 to 1.14, p = 0.53).

Relationship between heart rate at baseline and survival. In the univariable analysis restricted to patients in AF, each increase in resting heart rate of 10 beats/min was associated with a 7% decrease in mortality per year (HR: 0.93; 95%