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Aging and Heart Rate in Heart Failure: Clinical Implications for Long-term Mortality

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Abstract

Objective: To assess the relationship between resting heart rate and long-term all-cause mortality in ambulatory patients with heart failure (HF) relative to age, considering that although heart rate has been strongly associated with mortality in HF, the influence of age on target heart rate is incompletely characterized.

Patients and Methods: Consecutive patients in sinus rhythm referred to an ambulatory HF clinic of a university hospital between August 1, 2001, and March 31, 2012, were included. Unadjusted and adjusted Cox regression analyses were performed to assess heart rate as a prognostic marker, both as a continuous variable and after categorization into quintiles. Smooth spline estimates and hazard ratios (HRs) were plotted for 2 age strata (<75 years vs ≥75 years) for each individual heart rate.

Results: A total of 1033 patients were included (766 men [74.2%]; mean age, 65.1±12.6 years). During a mean follow-up of 4.6±3.3 years (median, 3.8 years [25th-75th percentile, 1.9-6.9]), 476 patients (46.1%) died. Mortality was associated with a statistically greater heart rate in the total cohort (HR, 1.18; 95% CI, 1.11-1.26; $P<.001$). From a clinical viewpoint, this means an 18% increased risk for every 10-beats/min elevation in heart rate. The same characteristics were present in the relationship between heart rate assessed after 6 months and long-term mortality (HR, 1.30; 95% CI, 1.20-1.42; $P<.001$). Overall, the prognostic importance of heart rate in ambulatory patients with HF was largely influenced by patient age. Remarkably, in the elderly population (≥75 years), heart rate below 68 beats/min conferred an increased risk of death, whereas in younger patients, mortality exhibited a declining slope at even the lowest heart rates.

Conclusion: Our research, if applicable to the prospective management of patients with ambulatory HF, suggests that patients aged 75 years or older have the best outcomes with target heart rates of 68 beats/min; however, younger patients may benefit from lower heart rates, even below 55 beats/min.

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Elevated resting heart rate is associated with the occurrence of cardiovascular complications and poor outcomes in different diseases, including heart failure (HF).[1] The current target of HF treatment is to reduce heart rate,[2,3] and the benefits of β-adrenergic–blocking drugs are thought to be due to such a reduction.[4] Data derived from clinical trials on β-blockers[5,6] suggest that the most determinant β-blocker effect is derived from the reduction in the heart rate rather than the drug dose. Alternative treatments with the goal of reducing heart rate, as with the β-adrenergic–independent angina pectoris treatment ivabradine, also improve the prognosis of patients with HF[7] and reaffirm this concept.[8] However, the influence of age on target heart rate is unknown because most of the studies that have assessed the influence of heart rate on HF prognosis have not included large numbers of elderly patients.[7,9] The same benefits of heart rate reduction are assumed to occur across all age strata, but this aspect has not been well studied.

Our aim was to assess the relationship between resting heart rate in ambulatory patients with HF in sinus rhythm (SR) and long-term

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all-cause mortality relative to age (<75 vs ≥75 years).

PATIENTS AND METHODS

Study Design and Population

All consecutive ambulatory patients referred to a structured HF clinic of a university hospital between August 1, 2001, and March 31, 2012, irrespective of etiology, were included in an outpatient setting. The criteria for clinical practice referral to the HF unit have been reported elsewhere.[10-12] Briefly, the criteria were HF with at least one hospitalization and/or reduced left ventricular ejection fraction (LVEF; <40%). Most patients were referred from cardiology and internal medicine departments, and fewer were from the emergency department/short-stay unit or other hospital departments. Less than 10% of patients were admitted to the HF unit because of asymptomatic reduced LVEF after acute myocardial infarction.

All patients were seen regularly during follow-up visits at the HF clinic according to their clinical needs. Follow-up visits included a minimum of one visit with a nurse every 3 months and one visit with a physician (cardiologist, internist, or family physician) every 6 months, as well as optional visits with specialists in geriatrics, psychiatry, and rehabilitation.[10-12] During their baseline visit, patients provided written consent for analytic samples and the use of their clinical data for research purposes. The study was performed in compliance with the law protecting personal data in accordance with the international guidelines on clinical investigation of the World Medical Association's Declaration of Helsinki.

At the patients' first visit, we recorded their demographic characteristics, baseline clinical status, physical examination data, and treatment following a standardized protocol. We performed 12-lead electrocardiography (ECG) in the supine position after 5 minutes of rest at the baseline visit and at every routine follow-up visit at established intervals at the unit. Cardiac rhythm and heart rates used for the analysis were taken from the recorded ECGs. Baseline heart rate was always obtained at the first visit between 9:00 AM and 11:00 AM; heart rate at 6 months was obtained between 8:30 AM and 2:30 PM, generally after breakfast and before lunch. All included patients had to be in SR irrespective of having a device with pacemaker function (patients with atrial pacing devices were excluded).

Death Assessment

Death from all causes was the main study outcome. The number and causes of death during follow-up were obtained from clinical records at the HF unit, other hospital departments, and other hospital records or by contacting the patient's relatives. Data were verified using the databases of the Catalan and Spanish Health System. Five patients were lost during follow-up and were adequately censored in the survival analysis.

Statistical Analyses

Categorical variables were described by frequencies and percentages. Continuous variables were described by mean ± SD or median and 25th through 75th percentiles (Q1-Q3) for cases with skewed distribution. Normal distribution was assessed with normal quantile-quantile plots. Statistical differences between groups were assessed using the χ^2 test for categorical variables, Student *t* test for continuous variables with normal distribution, or the Mann-Whitney *U* test for nonnormal distributions. Univariate Cox proportional hazards regression analysis was performed using all-cause mortality as the dependent variable and heart rate per every 10 beats/min (continuous) as the independent variable. This analysis was repeated after categorizing heart rate into quintiles, and Cox survival curves were plotted. A multivariate Cox proportional hazards model was created, adjusting for age, sex, New York Heart Association functional class, LVEF, etiology of HF, and treatment with β-blockers and ivabradine for heart rate per every 10 beats/min as a continuous variable and based on its quintiles. Changes in heart rate between the baseline and 6-month visits were categorized into 3 groups: significant decrease (reduction ≥15%), no change (−14% to +14%), and significant increase (increase ≥15%). Age-adjusted Cox regression analysis was also performed for these groups. Statistical analyses were performed using SPSS statistical software version 15 (SPSS Inc) and the R software version 2.11.1 statistical package (R Foundation for

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