Serial Heart Rates, Guideline-Directed Beta Blocker Use, and Outcomes in Patients With Chronic Heart Failure With Reduced Ejection Fraction

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A single heart rate (HR) measurement may inform future prognosis in chronic heart failure with reduced ejection fraction (HFrEF). The importance of elevated HR across serial assessment is uncertain, particularly with well-applied guideline-directed medical therapy (GDMT) with beta blockers (BBs). In this post hoc analysis of 129 patients with chronic HFrEF in sinus rhythm, who had aggressive medication titration over 10.6 months, HR and BB use were assessed at each visit (average of 6 visits per patient). All-cause mortality was assessed. At baseline, 81 subjects (62.8%) had HR ≥70 beats/min; 40 subjects (31.0%) had high HR despite being on ≥50% of GDMT BB dose. At final visit, 30.4% of the subjects still had high HR despite achieving ≥50% target BB dose. There were no significant baseline differences in demographics or BB doses in patients with HR <70 vs HR ≥70 beats/min. In adjusted model in which HR was treated as time-dependent covariate, an increase in HR of 10 beats/min was associated with an increased hazard of all-cause mortality during follow-up (adjusted hazard ratio per 10 beats/min = 2.46; 95% confidence interval 1.46–4.16, p <0.001). In conclusion, in well-managed patients with HFrEF, high HR was frequent even after aggressive medication titration, and often despite being on at least 50% of GDMT BB dose. An increase in HR was associated with worse clinical outcomes (Clinicaltrials.gov NCT#00351390). **(Am J Cardiol 2017;120:803–808)**

There is a growing recognition of the importance of heart rate (HR) control in patients with chronic heart failure with reduced ejection fraction (HFrEF) as an independent and modifiable predictor of risk. Traditionally, beta blockers (BBs) have been used as a part of guideline-derived medical therapy (GDMT) to reduce HR;[1–6] however, in patients with chronic HFrEF in sinus rhythm, ivabradine was recently added to the GDMT to reduce HR. Ivabradine is a specific inhibitor of the I_f current involved in sinoatrial nodal activity and reduces the HR.[7] In the Systolic HF Treatment with the I_f Inhibitor Ivabradine Trial (SHIFT) trial of 6,505 subjects with chronic HFrEF and HR ≥70 beats/min, ivabradine therapy added to GDMT resulted in significant improvement in HF hospitalization.[8] The frequency and trend of elevated HR in chronic HFrEF and how many patients may be eligible for ivabradine therapy remain uncertain. Thus, we evaluated serial HR, BB use, and cardiovascular outcomes in a contemporary cohort of patients on aggressive GDMT (Clinicaltrials.gov NCT#00351390).

Methods

One hundred twenty-nine patients in sinus or paced rhythm without atrial fibrillation or flutter on enrollment electrocardiogram (ECG) from the ProBNP Outpatient Tailored Chronic HF Therapy (PROTECT) study, a single-center, randomized, controlled trial that evaluated the use of N-terminal pro–B-type natriuretic peptide (NT-proBNP)-guided therapy (with a goal to reduce NT-proBNP ≤1000 pg/ml) added to standard of care (SOC) compared with SOC HF management in chronic HFrEF, were included and followed up for 10 ± 6 months.[9,10] Patients underwent aggressive titration of GDMT (ivabradine had not been approved at the time). The primary end point of the trial was total cardiovascular events, including worsening HF, hospitalization for HF, significant ventricular arrhythmia, and cardiac death. All patients in the trial gave their informed consent, and the study was approved by the Partners Healthcare Institutional Review Board and was in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

HR was recorded from each visit ECG while the patient was lying supine and at rest. The HR categorical cutoff of 70 beats/min was chosen based on published data and regulatory approvals.[8]

Blood samples were taken at each study visit and processed, and plasma or serum was stored at −80 °C. Concentrations of NT-proBNP, soluble ST2, and highly sensitive troponin T were measured as previously reported.[11–13]

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This work was performed at the Massachusetts General Hospital, Boston, Massachusetts.

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All BB doses were converted to total daily dose of metoprolol succinate-equivalent for ease of comparison for this analysis.[14] The 50% GDMT BB dose was considered 100 mg total daily metoprolol succinate-equivalent.

Categorical variables in HR groups were compared using the chi-square test or Fisher's exact test; continuous variables were compared using two-sample *t* test, Mann-Whitney U or Kruskal-Wallis test. Two-sample *t* test was used to compare differences in mean HR across study visits by treatment arm and age. Fisher's exact test was used to determine the percentage of subjects with a HR ≥ 70 beats/min across study visits and as a function of treatment arm and age <75 and ≥75 years. Patient visits were evaluated at each visit as well as quarterly. Percent time with HR < 70 beats/min was calculated by assuming constant HR until the next visit over follow-up time. Mixed-effects models with random effects for patient intercepts and slopes were used to assess for trends in HR over time while accounting for the repeated measurements per patient. If there were multiple visits within the time period, HR and BB doses were averaged.

Two clinical end points were considered: all-cause mortality and a composite of cardiovascular events (cardiovascular death, worsening HF, HF hospitalization, clinically significant ventricular arrhythmia, acute coronary syndrome, and cerebral ischemia). Cox proportional hazards models with HR as a time-varying covariate was used to analyze time-to-event data. Patients who did not experience an event were censored at the time of last contact or at the time of death. Six potential confounders (body mass index, gender, age, baseline BB dose, baseline estimated glomerular filtration rate, and baseline left ventricular ejection fraction [LVEF]) were included in the final adjusted model. Continuous biomarker variables were log-transformed before the analysis. In all statistical analyses, a 2-tailed $p < 0.05$ was considered statistically significant. All analyses were performed using the SAS Version 9.4 (SAS Institute, Cary, North Carolina).

Results

In this study, 129 patients were included with a total of 793 visits. The baseline characteristics are described (Table 1). Study participants with HR <70 beats/min were leaner (body mass index 27.6 kg/m^2 vs 29.9 kg/m^2, $p = 0.05$), less likely to be on digoxin (10% vs 28%, $p = 0.03$), and more likely to have better left ventricular systolic function (LVEF 29.7% vs 26.1%, $p = 0.04$) and lower highly sensitive troponin T concentration (14.7 pg/mL vs 25.5 pg/mL, $p = 0.03$) compared with those with HR ≥70 beats/min.

Although the average HR over time showed a statistically significant decrease over time (Table 2), there was no significant trend in within-patient HR over time (Figures 1 and 2). Patients <75 years of age tended to have higher HR than patients ≥75 years, but no such differences were observed when comparing patients by treatment arms across study visits (Supplementary Table S1). At 12 months, younger patients had a significant decrease in HR compared with the older patients (−7.2 vs 1.3, respectively, $p = 0.009$) (Supplementary Table S2). There were no important differences in the change in HR between SOC and NT-proBNP arms.

BB dose (with respect to GDMT) and HR were evaluated at baseline and final visit (Figure 3). At baseline, 81 patients (62.8%) had a HR ≥70 beats/min; 40 (31.0%) patients had a HR ≥70 beats/min despite being on at least 50% GDMT BB dose. At the final visit, 30.4% of the patients continued to have a HR ≥70 beats/min despite being on at least 50% of GDMT BB dose.

The percentage of patients with HR ≥70 beats/min, mean doses of BB, and percentage of patients with HR ≥70 beats/min on at least 50% of GDMT dose of BB were evaluated at quarterly time points (Table 2). Over time, mean HR tended to decrease ($p = 0.03$ for trend), BB dose appeared to increase but did not reach statistical significance ($p = 0.26$ for trend), whereas the percentage of patients with HR ≥70 beats/min on at least 50% of GDMT dose of BB did not show a clear trend ($p = 0.54$). There were no significant differences in patients in different treatment arms, but a more pronounced decrease in HR over time was found in patients <75 years of age (Supplementary Table S3).

When all the HRs are considered as a total over the entire follow-up for each patient, patients spent, on average, 46.8% of the follow-up time with HR <70 beats/min. Although there were no significant differences in the percent time with HR <70 beats/min in the two study arms, patient ages ≥75 years spent more percent time with lower HR than those younger than 75 years (65.3% vs 41.2%, $p = 0.004$).

In an adjusted model in which HR was treated as a time-varying covariate, an increase in HR of 10 beats/min was associated with an increase in risk of all-cause mortality during follow-up (adjusted hazard ratio = 2.46 per 10 beats/min increase in HR; 95% confidence interval [CI] 1.46–4.16, $p < 0.001$ and unadjusted hazard ratio = 2.06 per 10 beats/min increase in HR; 95% CI 1.39–3.05, $p < 0.001$). No statistically significant findings were observed for cardiovascular events.

In an exploratory analysis, HR trend over time appeared to be associated with the cardiovascular events but did not reach statistical significance; patients who had persistently lower HR (HR <70 beats/min at baseline and final study visit), and whose HR decreased over follow-up had lower cardiovascular event rates, whereas patients with persistently higher HR and whose HR increased over follow-up had higher cardiovascular event rates (Figure 4). There were not enough all-cause mortality to draw any conclusions regarding HF trend and all-cause mortality.

Discussion

In a population of well-managed patients with chronic HFrEF in sinus rhythm, there was a relatively small to no decrease in HR over time despite aggressive medical therapy. In addition, a significant portion of these patients were not able to achieve HR <70 beats/min despite being on aggressive GDMT. As might be expected, subjects with HR ≥70 beats/min had higher cardiovascular event rates, and increasing HR by study conclusion was associated with worse outcomes. Since the PROTECT study was performed, ivabradine was incorporated into clinical practice guidelines.[15] To the extent our study had a central message of aggressive medication titration, our results suggest a significant proportion of patients with chronic HFrEFs on GDMT BB may nonetheless benefit from further decreasing of HR even with assiduous application and titration of GDMT.