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Relationship of Elevated Heart Rate in Patients with Heart Failure with Reduced Ejection Fraction to One-Year Outcomes and Costs

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Abstract

There are limited data describing outcomes associated with an elevated heart rate in patients with heart failure with reduced ejection fraction (HFrEF) in routine clinical practice. We identified patients with HFrEF at Duke University Hospital undergoing echocardiograms and heart rate assessments without paced rhythms or atrial fibrillation. Outcomes (all-cause mortality or hospitalization and medical costs per day alive) were assessed using electronic medical records, hospital cost accounting data, and national death records. Patients were stratified by heart rate (<70, 70 bpm) and compared using generalized linear models specified with gamma error distributions and log-links for costs and proportional hazard models for mortality/hospitalization. Of 722 eligible patients, 582 (81%) were treated with beta-blockers. The median heart rate was 81 bpm (25th, 75th percentile 69–96) and 527 (73%) had a heart rate 70 bpm. After multivariable adjustment, a heart rate 70 bpm was associated with increased 1-year all-cause mortality or hospitalization, hazard ratio 1.37 (95% CI 1.07, 1.75) and increased medical costs per day alive, cost ratio 2.03 (95% CI 1.53, 2.69). In conclusion, at a large tertiary care center, despite broad use of beta-blockers, a heart rate 70 bpm was observed in 73% of patients with HFrEF and associated with worse 1-year outcomes and increased direct medical costs per day alive.

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Keywords

heart failure; heart rate; outcomes

Introduction

Given the recent United States Food and Drug Administration (FDA) approval of ivabradine, there is increased attention on identifying patients with heart failure with reduced ejection fraction (HFrEF) and elevated heart rate (HR) in routine practice. Elevated resting HR is an established risk factor for poor outcomes in patients with heart failure (HF),^{1–5} and results of the Systolic Heart Failure Treatment With Ivabradine Trial (SHIFT) demonstrated that HR reduction with ivabradine improved clinical outcomes for patients in sinus rhythm with chronic, symptomatic HFrEF and a HR $\geq$ 70 beats per minute (bpm).⁶ Previous evaluations of HR in patients with HFrEF in routine practice focused on patients hospitalized with HF^{4, 5, 7} or were performed outside the United States.^{8–10} In addition, there are limited data evaluating the association of HR $\geq$ 70 bpm with future medical costs. We aimed to describe the proportion of patients at a large tertiary care center in the United States with HRs $\geq$ 70 bpm and associated outcomes including mortality, hospitalizations, and costs.

Methods

Patients were first identified using the Duke Echocardiography Laboratory Database, which is a prospectively maintained digital archive of all clinical echocardiograms performed in the Duke University Health System (Durham, NC) since 1995 that is linked to a corresponding searchable reporting database. This database also contains information on HR obtained at the time of the echocardiogram. Additional information on heart rhythm was obtained from a linked repository of electrocardiograms performed at Duke University Medical Center. Baseline clinical variables, including demographics, laboratory data, medications, and International Classification of Disease, 9th Revision, Clinical Modification (ICD-9) codes, for each patient were also obtained from the searchable, online Duke Enterprise Data Unified Content Explorer research portal. Follow-up data were obtained from electronic medical records and the Duke Databank of Cardiovascular Disease, a databank of all patients who underwent a cardiac catheterization and/or cardiac surgery at Duke University Medical Center since 1969. Additional mortality data was obtained through a search of the Social Security Death Master File.¹¹ Institutional cost data was obtained from the medical center's cost accounting system (Allscripts EPSiTM), to provide direct and indirect costs for inpatient and outpatient care inclusive of laboratory testing, medical procedures and imaging. We also obtained professional billing records representing payments for all inpatient and outpatient services performed within 1 year of the index echocardiogram for each patient. The Institutional Review Board of the Duke University Health System approved this study.

For this analysis, we identified patients age 18 years or older who underwent an echocardiogram as either an inpatient or outpatient for HF between August 1, 2008 and July 31, 2010 and a recent linked electrocardiogram (i.e., within 6 months prior to the

echocardiogram). Patients were included if they were assigned an ICD-9 code for HF for any encounter within the 12 months prior to the echocardiogram. If a patient had > 1 echocardiogram performed during the study period, then we used the first as the index echocardiogram.

We excluded patients with a preserved left ventricular ejection fraction (LVEF) (>40%) as reported clinically by either quantitative or qualitative assessment. This definition was chosen to be consistent with recent guideline definitions of HFrEF.¹² Using data from the recent electrocardiograms patients with a paced rhythm or recent atrial fibrillation were excluded. If a patient had ≥ 1 electrocardiogram performed on the same day, each was reviewed for a paced rhythm or atrial fibrillation. We also limited the analysis to patients with expected follow-up at Duke University Medical Center, as defined by ≥ 2 outpatient visits within the medical center in the 18 months preceding the echocardiogram.

Heart rates used in the analysis were from a clinical assessment of HR performed at the beginning of the echocardiogram with the patient typically resting in the supine position. In the event this was missing, we used the HR measure from the most recent electrocardiogram performed within 6 months of the baseline echocardiogram.

We first described baseline characteristics of the study population stratified by resting HR (<70 bpm and ≥ 70 bpm). This cutoff was chosen to be consistent with the design of the SHIFT trial, which included patients with chronic, symptomatic HFrEF, HR ≥ 70 bpm, and background medical therapy that included a maximally tolerated dose of β-blocker therapy or a contraindication or intolerance to β-blocker therapy.⁶ We reported frequencies and proportions for categorical variables and medians with 25th, 75th percentiles for continuous variables. We compared the 2 groups using chi-square tests for categorical variables and Wilcoxon tests for continuous variables.

We then described and compared 1-year outcomes of interest by group, including a composite of all-cause mortality or hospitalization, all-cause mortality, all-cause hospitalization, and average medical costs per day alive. We used Cox proportional hazard models to compare time-to-event (i.e. mortality and/or hospitalization) endpoints, adjusting for potential confounding variables. Candidate variables were selected for use in the multivariable models based on clinical judgment. For adjusted comparisons of costs, we used a generalized linear model specified with a log link and gamma error distribution.

In a sensitivity analysis we restricted the cohort to those patient potentially eligible for ivabradine, i.e., an LVEF ≥ 35%. Given the smaller cohort we performed adjusted analysis using a parsimonious model and the full model used in the prior analyses.

We used 2-tailed $\alpha = .05$ to establish statistical significance and reported 95% confidence intervals. All analyses were performed using SAS software (version 9.2 or higher, SAS Institute, Cary, NC).

Results

Among 5,265 unique patients with HF undergoing an echocardiogram at Duke University Medical Center during the study period, 3413 (65%), were initially excluded for a preserved LVEF (Figure 1). The remaining were excluded for a recent paced rhythm, recent atrial fibrillation, or a missing electrocardiogram, 868 (16%), or for <2 recent outpatient visits at Duke University Medical Center, 260 (4.9%). Finally, a total of 724 unique patients met the study criteria of which 2 additional patients were excluded from the outcomes analysis due to incomplete cost data; rendering a final sample size of 722.

Baseline characteristics of the study population stratified by resting HR (<70 bpm or ≥70 bpm) are reported in Table 1. The median HR for the study population was 81 bpm (25th, 75th percentile 69–96) and 582 (81%) were on a beta-blocker. Patients with a HR ≥70 bpm were younger (median age 61 versus 66 years, $p<.001$), were less likely to have coronary artery disease (64% versus 75%, $p=.007$), and were more likely to have an LVEF<20% (17% versus 5.1%, $p<.001$) compared to those without. The echocardiogram was also more likely to be performed while hospitalized (63% versus 37%, $p<.001$) for patients with a HR ≥70 bpm compared to those without. Use of a beta-blocker was greater in patients with a HR ≥70 bpm compared to those without (82% versus 76%, $p=0.051$).

The association between a HR ≥70 bpm and 1-year outcomes including costs per day alive are shown in Table 2 and Figure 2 and Figure 3. A HR ≥70 bpm was associated with increased 1-year all-cause mortality or all-cause hospitalization in both unadjusted, hazard ratio 1.67 (95% CI 1.32, 2.09, $p<.001$) and adjusted analyses, hazard ratio 1.37 (95% CI 1.07, 1.75, $p=.012$). We found similar results for individual components of the 1-year outcome. A HR ≥70 bpm was also associated with increased medical costs per day alive in both unadjusted, cost ratio 3.37 (95% CI 2.81, 4.96, $p<.001$), and adjusted analyses, cost ratio 2.03 (95% CI 1.53, 2.69, $p<.001$). We also repeated the analysis considering heart rate as a continuous variable. A 10 bpm increase in HR was associated with increased 1-year all-cause mortality or all-cause hospitalization in both unadjusted, hazard ratio 1.15 (95% CI 1.10, 1.20, $p<.001$) and adjusted analyses, hazard ratio 1.11 (95% CI 1.05, 1.17, $p<.001$). Increasing heart rate was also associated with increased medical costs per day alive in both unadjusted, cost ratio 1.42 (95% CI 1.33, 1.51, $p<.001$), and adjusted analyses, cost ratio 1.32 (95% CI 1.24, 1.40, $p<.001$).

In sensitivity analyses of patients with LVEF ≥35% (Supplemental Table 1 and 2 and Figures) we found similar results for the composite endpoint of 1-year all-cause mortality or all-cause hospitalization and medical costs per day alive though the findings were somewhat attenuated. For the individual components of the composite endpoint, 1-year all-cause mortality and 1-year all-cause hospitalization, the association remained significant in a parsimonious model but not in the full model used for the primary analysis. We found no significant interaction between HR ≥70 bpm and echocardiogram while hospitalized for any of the outcomes. We also found no significant interaction between HR ≥70 bpm and beta-blocker use for all-cause mortality or hospitalization though beta-blocker use did attenuate the relationship between HR ≥70 bpm and medical costs per day alive.

Discussion

In this study, we used data from a large medical center in the United States to determine the proportion of patients with HFrEF that have HRs ≥ 70 bpm in routine clinical practice and to examine associated outcomes. Using a large database of patients undergoing echocardiograms, we found that most patients, 65%, had a preserved LVEF with no current HF indication for HR lowering therapies including beta-blockers or ivabradine. Of the remaining patients with sinus rhythm and HFrEF, 73%, had a HR ≥ 70 bpm despite a broad use of beta-blockers. Consistent with prior observational studies, we found that HR ≥ 70 bpm was associated with increased risk of all-cause mortality or all-cause hospitalization in this patient population.^{1–5, 7} To our knowledge, our study is the first to also note increased costs associated with HR ≥ 70 bpm in patients with HFrEF. After adjustment for known confounders we observed a twofold increase in costs per day alive in patients with a HR ≥ 70 bpm compared to those without. These data have important implications for HF programs and medical centers interested in adopting programs that target HRs ≥ 70 bpm in patients with HFrEF, for either titration of beta-blockers or the initiation of ivabradine.

Our findings on the prevalence of patients with HFrEF with HRs ≥ 70 bpm should be interpreted in the context of other similar observational studies, though these studies were performed outside the United States. In an analysis of HF patients with regular outpatient follow-up at a HF-specialty clinic at the University of Heidelberg, 20% of patients had sinus rhythm and symptomatic HFrEF, the remainder with HF with preserved ejection fraction and/or atrial fibrillation.⁸ Of patients with sinus rhythm and symptomatic HFrEF, the majority, 64%, had an elevated HR despite high use of guideline-directed medical therapy including 69% of patients on $\geq 50\%$ of target doses of beta-blockers. Of 1000 consecutive clinic visits at a HF-specialty clinic in Kingston-upon-Hull, United Kingdom, 17% of patients had HFrEF and sinus rhythm.¹⁰ In contrast to our study and the above data from Germany, a smaller proportion of these patients, $<20\%$, had elevated HRs during serial follow-up visits. However, in that study, the authors highlighted that more than half of the patients with opportunities for titration of beta-blockers or ivabradine were missed and no actions were taken to address the elevated HR at clinic visits. What is not clear from these data or our study, are the best practices for a clinic or health system to identify patients eligible for HR lowering therapies.

Our observation that a high proportion of patients with sinus rhythm and HFrEF have HRs ≥ 70 bpm may be related to the current doses of beta-blockers achieved in routine clinical practice. Currently, only 16–37% of patients are able to tolerate target doses of beta-blockers achieved in clinical trials.^{13–19} The reasons for this are likely related to differences in populations, especially when considering the younger age and fewer comorbid conditions of patients enrolled in clinical trials. However, given the current state of therapy, it is important to recognize that further HR lowering may be possible with aggressive titration of beta-blockers.

In our analysis we estimated medical costs associated with HRs ≥ 70 bpm in patients with HFrEF. Given that patients with an elevated HR have a well-described association with increased mortality, we focused on costs per day alive. Our findings were robust even when

restricting the population to those with an LVEF of $\geq 35\%$. Our results provide the rationale to support prospective evaluations of programs designed to identify patients with HFrEF with sinus rhythm and elevated HRs for increased medical therapies with the aim of improving HF outcomes and value of care. Such programs could take the form of traditional interventions such as office-based protocols developed for specialty HF clinics or more innovative interventions that harness existing and emerging technologies. For example, programs could be developed that incorporate 24-hour HR data from existing cardiac electronic implantable devices, such as implantable cardioverter defibrillators, or from HR monitors and other types of wearable devices. These data could be made available to providers via the electronic health record or delivered directly to patients along with education on available treatment strategies. In addition to providing a more comprehensive assessment of HR, incorporating these types of technology-based solutions offer the opportunities for scalable and reproducible programs.

In addition to being single-center and retrospective, our study has limitations. The HR used for our analysis was taken from single clinical assessments though this is also the method currently used in routine practice. We also considered both inpatients and outpatients in our study though the physiology of these 2 patient populations is different. We adjusted for inpatient setting in our multivariable analysis though it is possible our findings may have differed if we restricted the population to inpatients or outpatients. The clinical database used for our analysis also does not provide dosing information for beta-blockers. Therefore, we do not know the doses of medications taken at the time of HR assessment and were unable to consider this in our analysis.

At a large tertiary care center, despite broad use of beta-blockers, HR ≥ 70 bpm was observed in 73% of HFrEF patients without paced rhythms or recent arrhythmias. As opposed to HFrEF patients with lower HRs, HFrEF patients with higher HRs experienced significantly higher risk of mortality and/or hospitalizations at 1 year and incurred higher direct medical costs per day alive. Future studies are needed to evaluate the effectiveness and value of interventions used to identify patients with elevated HRs that are eligible for HR lowering therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Flow Diagram of the Study Design. This figure displays the initial study population, through exclusions, to the final study population. DUMC indicates Duke University Medical Center and ECG indicates electrocardiogram

Figure 2.

Kaplan-Meier curves for the probability of all-cause mortality or all-cause hospitalization. This figure displays the Kaplan-Meier estimated event rate for all-cause mortality or all-cause hospitalization

Figure 3.

Kaplan-Meier curves for the probability of all-cause mortality. This figure displays the Kaplan-Meier estimated event rate for all-cause mortality

Table 1Baseline characteristics stratified by heart rate ≥ 70 beats/min

	All (N=722)	Heart Rate (bpm)		
Variable		<70 (N=195)	70 (N=527)	p-value
Age, years, median (25th, 75th)	62 (52, 73)	66 (58, 75)	61 (49, 71)	<.001
Women	264 (37%)	60 (31%)	204 (39%)	0.049
White	398 (55%)	120 (62%)	278 (53%)	
Black	308 (43%)	68 (35%)	240 (46%)	
Asian	4 (0.6%)	1 (0.5%)	3 (0.6%)	
Other race or ethnicity	7 (1.0%)	3 (1.5%)	4 (0.8%)	
Coronary artery disease	485 (67%)	146 (75%)	339 (64%)	0.007
Prior stroke or transient ischemic attack	143 (20%)	45 (23%)	98 (19%)	0.18
Peripheral arterial disease	128 (18%)	43 (22%)	85 (16%)	0.064
Diabetes mellitus	320 (44%)	72 (37%)	248 (47%)	0.015
Hypertension	599 (83%)	166 (85%)	433 (83%)	0.347
Hyperlipidemia	442 (61%)	136 (70%)	306 (58%)	0.004
Chronic kidney disease	232 (32%)	55 (28%)	177 (34%)	0.169
Chronic obstructive pulmonary disease	83 (12%)	16 (8.2%)	67 (13%)	0.092
Obstructive sleep apnea	123 (17%)	26 (13%)	97 (18%)	0.107
Echo performed while hospitalized	405 (56%)	72 (37%)	333 (63%)	<.001
Baseline Evaluation				
Heart rate (bpm) median (25th, 75th)	81 (69, 96)	63 (57, 66)	89 (78, 103)	<.001
SBP (mm Hg) median (25th, 75th)	117 (103, 134)	130 (127, 142)	112 (102, 128)	0.016
NT-proBNP (pg/mL) median (25th, 75th)	3254 (1004, 9729)	1561 (434, 4353)	4029 (1351, 11,074)	<.001
LVEF (%) median (25th, 75th)	30 (20, 35)	30 (25, 36)	30 (20, 35)	0.001
LVEF<20%	97 (13%)	10 (5.1%)	87 (17%)	<.001
Creatinine (mg/dL) median (25th, 75th)	1.3 (1.0, 1.8)	1.2 (1.0, 1.7)	1.3 (1.0, 1.9)	0.215
Recent Medical Therapy				
ACE-inhibitor or ARB	533 (74%)	136 (70%)	397 (75%)	0.129
Beta blocker	582 (81%)	148 (76%)	434 (82%)	0.051
Aldosterone antagonist	198 (27%)	43 (22%)	155 (29%)	0.049
Digoxin	97 (13%)	23 (12%)	74 (14%)	0.432
Hydralazine	176 (24%)	40 (21%)	136 (26%)	0.141
Long-acting nitrates	172 (24%)	41 (21%)	131 (25%)	0.283

ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BPM = beats per minute; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SBP = systolic blood pressure

Table 2

Association between heart rate > 70 beats/min and 1-year outcomes

	Unadjusted		Adjusted*	
1-Year Outcomes	HR (95% CI)	p-value	HR (95% CI)	p-value
Mortality or Hospitalization	1.67 (1.32 to 2.09)	<.001	1.37 (1.07 to 1.75)	0.012
Mortality	2.32 (1.51 to 3.58)	<.001	1.78 (1.13 to 2.80)	0.013
All-Cause Hospitalization	1.54 (1.20 to 1.98)	0.001	1.32 (1.01 to 1.72)	0.043
	Cost Ratio (95% CI)	p-value	Cost Ratio (95% CI)	p-value
Average Medical Cost per Day Alive	3.37 (2.81 to 4.96)	<.001	2.03 (1.53 to 2.69)	<.001

HR = hazard ratio.

* Adjusted for age, gender, race, echocardiogram performed during a hospitalization, chronic obstructive pulmonary disease, diabetes mellitus, hyperlipidemia, previous stroke or transient ischemic attack, chronic kidney disease, obstructive sleep apnea, coronary artery disease, beta-blocker use, left ventricular ejection fraction, and creatinine. The reference group is patients with heart rate <70 beats/min.