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Differential impact of heart rate and blood pressure on outcome in patients with heart failure with reduced versus preserved left ventricular ejection fraction ☆

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ABSTRACT

Background: In contrast to patients with heart failure (HF) with reduced left ventricular ejection fraction (LVEF; HFREF) the prognostic role of heart rate (HR) and blood pressure (BP) in patients with HF and preserved LVEF (HFPEF) is not well known. The aim of this study was to characterize the relationship between HR and BP and outcomes in HFPEF and to compare it to HFREF.

Methods: The association between HR and BP and outcomes (median follow-up: 38 months) was analyzed in patients with HFREF (LVEF≤45%; n=6792) and HFPEF (LVEF>45%; n=988) from the Digitalis Investigator Group trial.

Results: Mortality (35% vs. 23%) and HF hospitalization rates (31% vs. 20%; p<0.001 for both) were higher in HFREF compared to HFPEF. In HFREF, higher HR and lower systolic and diastolic BP quartiles were associated with higher mortality and HF hospitalization rates. By contrast, there was no significant association between HR and BP respectively and mortality in HFPEF, and there was no significant association between systolic BP and hospitalization risk in HFPEF either. However, HF hospitalization rates were significantly related to increasing HR and decreasing diastolic BP quartile respectively (4.9, 6.8, 6.8, and 10.5 and 5.5, 8.1, 6.0, and 10.1 respectively events per 1000 person-years) in HFPEF. In HFPEF, there was also evidence of a significant J-shaped relationship between pulse pressure and mortality.

Conclusions: The prognostic value of HR and BP differed substantially between HFREF and HFPEF. These data may provide a foundation for the design of novel interventions in HFPEF patients.

1. Introduction

Several well validated prognostic models [1,2] have been developed for the estimation of risk in patients with heart failure (HF) and reduced left ventricular ejection fraction (LVEF; HFREF). Among the contributory parameters, simple hemodynamic indices, including lower systolic blood pressure (BP) [2] and a higher resting heart rate (HR) [3], have been shown to be associated with an increased mortality in these patients. Pathophysiologically, these two measures are reflective of reduced cardiac output and elevated cardiac adrenergic drive [4], which also correlate with survival in patients with HFREF [5]. In this context, renin–angiotensin system inhibition has been shown to improve cardiac output and β-antagonists to reduce HR in patients with HFREF, and both classes of agents are well known to improve prognosis in these patients [4].

By contrast, it remains uncertain whether a similar relationship exists between HR or BP and outcome in patients with HF and preserved LVEF (HFPEF). Similar to that for HFREF, the clarification of the nature and extent of an association between HR or BP and prognosis in these patients holds substantial importance, particularly given ongoing controversy about the pathophysiology of HFPEF and the relative failure of therapies with proven efficacy in HFREF [6–9].

Accordingly, the aim of the present study was to compare the relationship between HR and BP with outcome in a large cohort of HFREF and HFPEF patients that contributed to the Digitalis Investigations Group (DIG) trial.

2. Materials and methods

2.1. Participants

The present study is a *post hoc* analysis of the randomized DIG trial [10] performed using the study database obtained from the National Heart, Lung, and Blood Institute (NHLBI; website https://biolincc.nhlbi.nih.gov/studies/dig/). Patients with a clinical diagnosis of HF and LVEF≤45% or >45% and "probable diastolic HF" [11] recruited

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between January 1991 and August 1993 in the United States and Canada were included in the main or an ancillary trial parallel to the main trial. We labeled this group as HFPEF rather than HFNEF, given that the LVEF cutoff in the DIG trial was 45%. Methods and results of the main DIG trial [10] and the ancillary trial [12] have been previously reported in the detail. In the present analysis, all patients treated with digoxin or placebo from the main (n = 6792; 99.9%) and the ancillary (n = 988; 100%) trial with available baseline HR and systolic BP data were included.

The use of angiotensin converting enzyme inhibitors (ACEI) as background therapy was strongly encouraged for all patients with LVEF<45%. The use of β-blockers in HF was not well established at the time of recruitment and was not recorded. LVEF was determined by radionuclide ventriculography (65%), echocardiography (29%), or contrast left ventriculography (6%).

2.2. Follow-up and end points

The median (interquartile range) follow-ups in the main and ancillary trial were 37.8 (27.6–46.7) and 38.5 (30.6–46.7), respectively, months. The vital status of all patients was collected up to December 31, 1995. The primary end points of the analysis were total mortality and HF hospitalizations.

2.3. Statistical analysis

The baseline characteristics and outcomes of patients with HFREF and HFPEF were compared using χ^2 tests, unpaired *t*-tests, Mann–Whitney–U tests, and Kaplan–Meier estimates and log rank tests, respectively. We then performed analyses separately for the HFREF and HFPEF cohorts. Outcomes between patients in different baseline HR, systolic BP, diastolic BP, and pulse pressure (PP) quartiles were compared using Kaplan–Meier estimates and log rank tests. We then used a multivariable Cox proportional hazard regression analysis to determine the association between HR, systolic BP, diastolic BP, and PP quartiles and outcomes. Unadjusted hazard ratios and hazard ratios adjusted for age, gender, race (white–non-white), LVEF, estimated glomerular filtration rate, [13] HF etiology (ischemic–non-ischemic), New York Heart Association class, the presence or absence of diabetes and angina, non-potassium sparing diuretic use, digoxin treatment status (active–placebo), and systolic and diastolic BP or HR, respectively (depending on the dependent variable), were calculated. Analysis was performed using a commercially available software package (SPSS, version 15.0, Inc., Chicago, Illinois, USA).

3. Results

3.1. Clinical characteristics of patients with HFREF and HFPEF

Patients with HFREF and HFPEF differed substantially at baseline, as shown in Table 1. Besides other differences, patients with HFREF had higher HR, lower systolic and diastolic BP, and lower PP.

Table 1
Baseline characteristics of patients with heart failure (HF) and reduced left ventricular ejection fraction (LVEF; HFREF) and HF and preserved LVEF (HFPEF).

	HFREF (n = 6792)	HFPEF (n = 988)	P value
Age (years)	63 ± 11	67 ± 10	<0.001
Male gender	5275 (78)	581 (59)	<0.001
White race	5802 (85)	851 (86)	0.56
Ischemic HF etiology	4799 (71)	557 (56)	<0.001
Previous myocardial infarction	4416 (65)	489 (49)	<0.001
Duration HF (months)	17 (5–42)	15 (5–36)	0.02
LVEF (%)	29 ± 9	55 ± 8	<0.001
eGFR (mL/min/1.73 m^2)	60 ± 19	58 ± 19	0.01
Diabetes	1929 (28)	285 (29)	0.77
Angina	1819 (27)	294 (30)	0.05
NYHA class			<0.001
I	906 (13)	196 (20)	
II	3662 (54)	573 (58)	
III	2077 (31)	206 (21)	
IV	142 (21)	12 (1)	
Heart rate (bpm)	79 ± 13	76 ± 12	<0.001
Systolic blood pressure (mmHg)	126 ± 20	138 ± 21	<0.001
Diastolic blood pressure (mmHg)	75 ± 11	77 ± 11	<0.001
Pulse pressure (mmHg)	51 ± 16	61 ± 19	<0.001
Treatment			
Digoxin	3392 (50)	492 (50)	0.93
Potassium-sparing diuretics	516 (26)	79 (8)	0.66
Non-potassium-sparing diuretics	5317 (78)	751 (76)	0.10
Angiotensin converting enzyme inhibitors	6415 (94)	852 (86)	<0.001
Nitrates	2894 (43)	389 (39)	0.05
Hydralazine	141 (2)	17 (2)	0.46
Outcome			
Death	2373 (35)	231 (23)	<0.001
Cardiac death	1793 (26)	146 (15)	<0.001
Death in the context of worsening HF	843 (12)	64 (6)	<0.001
Cardiovascular death	1888 (28)	162 (16)	<0.001
Non-cardiovascular death	355 (5)	55 (6)	0.66
Death due to unknown reason	130 (2)	14 (1)	0.28
Hospitalization for worsening HF	2088 (31)	197 (20)	<0.001

Data are presented as number (percentages), mean ± standard deviation or median (interquartile range) as appropriate.
eGFR: estimated glomerular filtration rate.

3.2. Outcome in HFREF and HFPEF

Patients with HFREF had higher all-cause mortality and a higher HF hospitalization risk than HFPEF patients, and cardiac and cardiovascular mortality was also higher in HFREF patients (p<0.001 for all comparisons using log rank tests or χ^2 tests, as shown in Table 1), while non-cardiovascular mortality was similar between the groups.

3.3. Prognostic value of HR

In HFREF, higher HR was associated with a higher risk of death (Fig. 1A) and HF hospitalization (Fig. 1B). As shown in Table 2, patients in the highest HR quartile (>87 bpm) had a 31% higher risk of death compared to those in the lowest quartile (<71 bpm). After adjusting for other baseline variables, the risk of death remained significantly higher in patients in the highest compared to the lowest HR quartile. The adjusted hazard ratio for hospitalization for HF was significantly higher in patients in the third and fourth compared to the first HR quartile (Table 2).

In patients with HFPEF, there was no significant association between HR and mortality (Fig. 1C). However, there was a significant association between higher HR quartile and higher HF hospitalization risk (Fig. 1D). As shown in Table 2, patients in the highest HR quartile (>82 bpm) had more than double the risk of hospitalization for HF than those in the lowest HR quartile (<67 bpm). This association remained significant after adjusting for other patients characteristics, including digoxin treatment status.

3.4. Prognostic role of systolic BP

In HFREF, lower systolic BP was associated with a higher risk of mortality (Fig. 2A). The risk of HF hospitalization also differed significantly between different systolic BP quartiles (Fig. 2B) in HFREF. The HF hospitalization risk was the lowest in those in the third (123–139 mmHg) and the highest (44% higher than in the third quartile) in those in the lowest quartile (<111 mmHg).

In patients with HFPEF, there was no significant association between systolic BP and mortality (Fig. 2C) and HF hospitalization (Fig. 2D) (Table 3).

3.5. Prognostic role of diastolic BP

In HFREF, there was a strong association between lower diastolic BP and higher mortality (Fig. 3A) and HF hospitalization (Fig. 3B). As shown in Table 4, the risk of death was 70% higher in patients in the lowest compared to those in the highest quartile. Patients in the lowest quartile had a 49% higher risk of hospitalization for HF compared to those in the highest quartile. These associations