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Predictive value of early-phase heart rate reduction for subsequent recovery of left ventricular systolic function in heart failure with reduced ejection fraction

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Abstract

Introduction: *Predictors of heart failure with recovered ejection fraction (HFrecEF) remain to be fully elucidated. This study investigated the impact of heart rate and its change on the recovery of left ventricular ejection fraction (LVEF) in heart failure with reduced ejection fraction (HFrEF).*

Methods: *From 398 outpatients who had a history of hospitalisation for heart failure, 138 subjects diagnosed as HFrEF (LVEF < 40%) on heart failure hospitalisation were enrolled and longitudinally surveyed. During follow-up periods more than one year, 64 and 46 patients were identified as HFrecEF (improved LVEF to ≥ 40% and its increase of ≥ 10 points) and persistent HFrEF, respectively.*

Results: *In the overall subjects, the reduction of heart rate through the observation periods was closely correlated with the improvement of LVEF ($r = –0.508$, $p < 0.001$). Heart rate on hospital admission for heart failure was markedly higher in patients with HFrecEF (112 ± 26 bpm) than in those with persistent HFrEF (90±18 bpm). Whereas heart rate at the first outpatient visit after discharge was already lower in the HFrecEF group (80 ± 13 vs. 85 ± 13 bpm in the persistent HFrEF group). A multivariate logistic regression analysis revealed that the decrease in heart rate from admission to the first visit after discharge was a significant determinant of HFrecEF ($p < 0.001$), independently of confounding factors such as ischemic heart disease and baseline LVEF and left ventricular dimension.*

Conclusions: *Our findings suggest that heart rate reduction in the early phase after heart failure onset is a powerful independent predictor of the subsequent recovery of LVEF in HFrEF patients.* (Cardiol J 2024; 31, 4: 528–537)

Keywords: heart failure, ejection fraction, improvement, heart rate

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Introduction

The current guidelines divide heart failure patients into 3 categories on the basis of left ventricular ejection fraction (LVEF): heart failure with reduced ejection fraction (HFrEF, LVEF < 40%), with preserved ejection fraction (HFpEF, LVEF ≥ 50%), and with mid-range (or mildly reduced) ejection fraction (LVEF ≥ 40 and < 50%) [1, 2]. However, some patients with HFrEF experience a significant improvement of LVEF, termed heart failure with recovered (or improved) ejection fraction (HFrecEF) [3]. Because it has been revealed that patients with HFrecEF have a better prognosis than those with no subsequent LVEF improvement (i.e., persistent HFrEF) [4–9], early identification of patients who have the potential to recover their LVEF among those with HFrEF would be helpful for making therapeutic strategies and estimating their prognosis for heart failure patients. However, the background and pathophysiology of HFrecEF are considered to be very diverse [3], and it is speculated that various factors could be a predictor of HFrecEF.

Several large-scale clinical studies have shown that elevated resting heart rate is associated with higher morbidity and mortality in heart failure patients with systolic dysfunction [10–14]. Conversely, it is widely accepted that β-blocker therapy contributes to the recovery of decreased ventricular contractility and reduces mortality in patients with HFrEF through inhibition of sympathetic nerve activity and reduction of heart rate [14–17]. In addition, heart rate reduction with ivabradine, a specific I_f-channel inhibitor, has also been shown to be effective in both reversing left ventricular remodeling and improving cardiovascular prognosis in HFrEF patients [11, 18–21]. This suggests that heart rate reduction in the early phase after the onset of heart failure might be linked to subsequent recovery of left ventricular contraction in HFrEF. However, it has not been satisfactorily elucidated how heart rate and its change during hospitalization for heart failure are associated with the improvement of cardiac systolic function in patients with HFrEF. In particular, there has been no study examining the predictive value of heart rate change in the early phase of heart failure onset for subsequent recovery of LVEF in HFrEF. Therefore, the present study was designed to verify the hypothesis that early-phase heart rate reduction may be a significant predictor of HFrecEF in patients diagnosed as HFrEF at the index heart failure hospitalization.

Methods

Study subjects

From 396 chronic heart failure patients with a history of heart failure hospitalization who periodically visited outpatient clinic of the Department of Cardiovascular Medicine of our hospital in 2018, 138 patients with HFrEF (LVEF < 40%) at the index heart failure hospitalization were enrolled and longitudinally surveyed. Fourteen cases with no follow-up echocardiographic data at the time of ≥ 1 year after the initial assessment at the index heart failure hospitalization were excluded from the study. From 55 persistent HFrEF candidates with LVEF of < 40% after ≥ 1 year of follow-up, 9 patients with transient LVEF of ≥ 40% within one year of follow-up (i.e., those with fluctuating LVEF) were excluded. In addition, from 69 HFrecEF candidates with LVEF of ≥ 40% after ≥ 1 year of follow-up, 5 patients with its absolute increase of < 10 points from baseline LVEF were excluded in accordance with a definition newly proposed by the Committee of the Universal Definition of Heart Failure [2]. Ultimately, 46 patients with persistent HFrEF and 64 with HFrecEF were selected as eligible for the present analyses (Fig. 1).

All procedures of the present study were carried out in accordance with the principles outlined in the Declaration of Helsinki and national ethical guidelines for human studies. The study protocol was approved by the Ethics Committee of Ishikiriseiki Hospital (approval number: 21–21).

Echocardiography

In comparison of echocardiographic data between the 2 groups with persistent HFrEF and HFrecEF, findings in the initial assessment during the index heart failure hospitalization and in the first examination after ≥ 1 year of follow-up (as the data at the end of follow-up) were used for the present analyses. Comprehensive two-dimensional transthoracic echocardiography was performed using a cardiac ultrasound unit (Vivid 7; General Electric, Milwaukee, Wisconsin, USA) as previously described [22]. Measurements included left ventricular diameters at end-diastole (LVDd) and end-systole (LVDs), left atrial (LA) diameter, and inferior vena cava diameter at end-expiratory phase. LVEF was essentially measured using a modified Simpson's method.

Clinical parameters

We evaluated physical and laboratory findings and medication data at (or just before) discharge

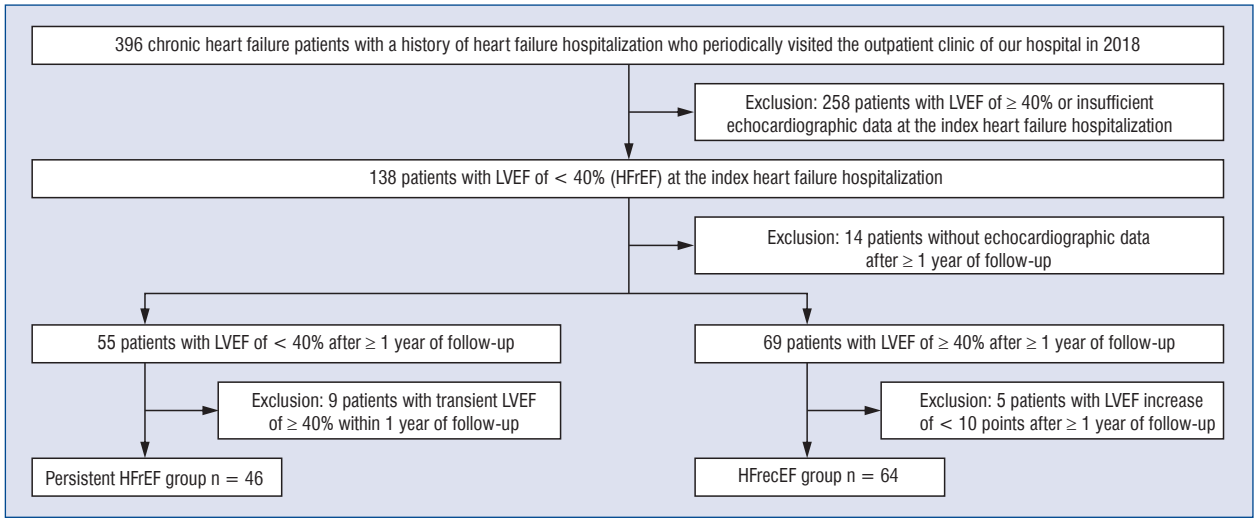

Figure 1. Flowchart of patients included in the present study. LVEF — left ventricular ejection fraction; HFrEF — heart failure with reduced ejection fraction; HFrecEF — heart failure with recovered ejection fraction

of the index heart failure hospitalization and at the outpatient visit just before the last echocardiographic examination as the end of follow-up. To assess changes in heart rate over time through the follow-up period, its values at the time of admission of the index heart failure hospitalization, at the first outpatient visit after discharge, and at the time of the last echocardiographic examination were also collected. The estimated glomerular filtration rate (eGFR) was calculated using a formula taken from the Modification of Diet in Renal Disease Study with a modified equation for Japanese subjects [23]. Plasma brain natriuretic peptide (BNP) was measured with a specific immunoradiometric assay for human BNP (ARCHIECT-JP, ABBOT JAPAN Co, Ltd, Tokyo, Japan) [24]. The β-blocker dose was calculated using a carvedilol equivalent, which was defined as 20 mg of carvedilol being equivalent to 5 mg of bisoprolol [1].

Statistical analysis

Statistical analysis was performed using a standard statistical package (JMP 9.0; SAS Institute, Cary, North Carolina, USA). Values were expressed as mean ± SD. The significance of differences in various parameters between the 2 groups with persistent HFrEF and HFrecEF was evaluated with an unpaired Student's t-test. The simple correlation between variables was assessed using a univariate linear regression analysis and Pearson's correlation coefficient. A multiple logistic regression analysis was performed to identify factors independently associated with HFrecEF. Receiver operating characteristics were generated from multiple sensitivity/specificity pairs. The cutoff value of heart rate reduction to predict HFrecEF was chosen when the accuracy was maximized. A value of $p < 0.05$ was accepted as statistically significant.

Results

The baseline characteristics in the overall subjects and the 2 groups based on heart failure phenotypes are summarized in Table 1. Age and gender did not differ between the 2 groups with persistent HFrEF and HFrecEF. In addition, there was no difference in observation periods (i.e., days from the initial echocardiographic assessment at the index heart failure hospitalization to its examination after ≥ 1 year of follow-up as the end of follow-up) between the 2 groups (587 ± 215 and 607 ± 193 days in the persistent HFrEF and HFrecEF groups, respectively). As for causes of heart failure, ischemic heart disease was significantly more common in the persistent HFrEF group, while the rate of tachyarrhythmia was higher in the HFrecEF group.

Table 2 shows the comparison of clinical findings including electrocardiographic and echocardiographic data and medications at the index heart failure hospitalization between the 2 groups with persistent HFrEF and HFrecEF. In electrocardiographic findings on admission, the rate of subjects with atrial fibrillation rhythm was significantly higher in the HFrecEF group than in the persistent HFrEF group, and heart rate was markedly increased in patients with HFrecEF. Although there was no difference in LVEF on echocardiography at

Table 1. Baseline characteristics in the overall subjects and the 2 groups based on heart failure phenotypes

	All HFrEF (n = 110)	Persistent HFrEF (n = 46)	HFrecEF (n = 64)	P-value
Age, years	63.9 ± 11.8	63.6 ± 12.7	64.1 ± 11.2	0.851
Gender (men)	75%	74%	77%	0.753
Body mass index, kg/m^2	23.7 ± 4.9	24.7 ± 5.4	23.0 ± 4.4	0.071
Cause of heart failure (underlying disease)				
Ischemic heart disease	33%	57%	16%	< 0.001
Cardiomyopathy	38%	43%	34%	0.337
Valvular heart disease	6%	9%	5%	0.400
Tachyarrhythmia†	25%	9%	38%	< 0.001
Hypertensive	8%	2%	13%	0.052
Comorbidities				
Hypertension	65%	57%	72%	0.097
Dyslipidemia	52%	70%	39%	0.001
Diabetes mellitus	36%	52%	25%	0.003
Atrial fibrillation	46%	39%	52%	0.201
Peripheral artery disease	5%	9%	2%	0.078
Stroke	9%	15%	5%	0.059
Previous PCI	19%	39%	5%	< 0.001
Previous CABG	4%	9%	0%	0.016
Previous valve surgery	3%	7%	0%	0.039

Values are mean ± SD or percentage. CABG — coronary artery bypass grafting; HFrEF — heart failure with reduced ejection fraction; HFrecEF — heart failure with recovered ejection fraction; PCI — percutaneous coronary intervention; †All 28 patients had atrial tachyarrhythmias; 27 with atrial fibrillation (including intermittent atrial flutter in 4 patients) and one with atrial tachycardia

baseline between the two groups, LVDd and LVDs were significantly smaller in the HFrecEF group than in the persistent HFrEF group. In physical findings evaluated at discharge of the index heart failure hospitalization, the difference in heart rate found at the time of admission between the 2 groups disappeared. The rate of patients with atrial fibrillation was also no longer different between the 2 groups at the time of discharge, reflecting recovery to sinus rhythm from atrial tachyarrhythmias, which were more common in the HFrecEF group. As for medications at discharge, various drugs involved in the treatment of heart failure, including β-blocker and its dose (carvedilol equivalent dose), were used almost equally between the 2 groups.

Table 3 shows the comparison of treatment during follow-up and clinical findings and medications at the end of follow-up between the 2 groups with persistent HFrEF and HFrecEF. In electrocardiographic findings at the end of follow-up, the prevalence of atrial fibrillation rhythm did not significantly differ between the 2 groups with persistent HFrEF and HFrecEF. Heart rate was significantly decreased in the HFrecEF group than in the persistent HFrEF group. As a matter of course, LVEF markedly increased (from 27.9 ± 5.9 to 52.6 ± 7.4%) in the HFrecEF group compared with that in the persistent HFrEF group (from 26.8 ± 5.7 to 29.9 ± 5.1%). There was no difference in medication use between the 2 groups at the end of follow-up, as at discharge of the index heart failure hospitalization. It is noted that no patients in the HFrecEF or persistent HFrEF group received ivabradine throughout the follow-up.

The relation between respective changes in heart rate and LVEF throughout the follow-up period (from the time of admission of the index heart failure hospitalization) in the overall subjects is shown in Fig. 2A. The reduction of heart rate was significantly correlated with the improvement of LVEF ($r = -0.508$, $p < 0.001$). Figure 2B represents changes in heart rate over time through the follow-up period in patients with persistent HFrEF and HFrecEF. Heart rate at the time of admission of the index hospitalization was markedly increased in patients with HFrecEF compared with those with persistent HFrEF, but its values in the 2 patient groups became almost equal at the time of

Table 2. Comparison of clinical findings and medications at the index heart failure hospitalization between the 2 groups

	Persistent HFrEF (n = 46)	HFrecEF (n = 64)	P-value
ECG and UCG findings (on admission)			
Heart rhythm (atrial fibrillation)	22%	44%	0.018
Heart rate [bpm]	90 ± 18	112 ± 26	< 0.001
CLBBB	9%	10%	0.884
QRS duration [msec]	113 ± 27	103 ± 21	0.024
LVEF [%]	26.8 ± 5.7	27.9 ± 5.9	0.316
LVDd [mm]	61.1 ± 8 .3	57.3 ± 6.6	0.009
LVDs [mm]	53.1 ± 8.4	49.1 ± 7.0	0.008
LA diameter [mm]	46.3 ± 6.1	44.4 ± 6.7	0.127
IVC diameter [mm]	18.2 ± 5.3	18.7 ± 5.2	0.622
Physical and laboratory findings and medications (at discharge)			
Systolic blood pressure [mmHg]	114 ± 12	112 ± 14	0.512
Diastolic blood pressure [mmHg]	69 ± 11	67 ± 10	0.579
Heart rate [bpm]	75 ± 11	74 ± 12	0.673
Heart rhythm (atrial fibrillation)	17%	30%	0.142
Creatinine [mg/dL]	1.09 ± 0.98	0.98 ± 0.41	0.428
eGFR [mL/min/1.73 m^2]	65.3 ± 28.1	63.7 ± 23.2	0.740
BNP [pg/mL]	431 ± 390	257 ± 279	0.015
β-blocker	91%	94%	0.584
β-blocker dose [mg/day*]	7.9 ± 5.5	6.8 ± 4.3	0.267
RAS inhibitor	64%	66%	0.834
MR antagonist	57%	63%	0.558
Loop diuretic	80%	81%	0.828
Digitalis	7%	5%	0.639
Amiodarone	25%	16%	0.230

Values are mean ± SD or percentage. BNP — brain natriuretic peptide; CLBBB — complete left bundle branch block; ECG — electrocardiography; eGFR — estimated glomerular filtration rate; HFrEF — heart failure with reduced ejection fraction; HFrecEF — heart failure with recovered ejection fraction; IVC — inferior vena cava; LA — left atrial; LVDd — left ventricular diameter at end-diastole; LVDs — left ventricular diameter at end-systole; LVEF — left ventricular ejection fraction; MR — mineralocorticoid receptor; RAS — renin-angiotensin system; UCG — ultrasound echocardiography. *Carvedilol equivalent dose; i.e., bisoprolol 5 mg was considered equivalent to carvedilol 20 mg

discharge. Furthermore, at the first outpatient visit after discharge, heart rate in the HFrecEF group was significantly lower than that in the persistent HFrEF, and this difference in heart rate between the 2 groups was sustained until the end of follow-up (i.e., the last echocardiographic examination). The trends in heart rate changes over time through the follow-up period observed in the 2 groups were similar even when reexamined only in patients without tachyarrhythmia as a cause of heart failure (Suppl. Fig. S1).

We examined which factor was strongly associated with HFrecEF among heart rhythm and heart rate on hospital admission for heart failure and early-phase heart rate reduction. As shown in Table 4, heart rate reduction-2, i.e., the reduction of heart rate from on admission of heart failure hospitalization to the first outpatient visit after discharge, was most significantly associated with HFrecEF in the multivariate analysis. In a receiver operating characteristic analysis, the best cutoff value of heart rate reduction-2 to predict HFrecEF as distinguished from persistent HFrEF was 19.5 bpm and its area under the curve was 0.799. Finally, the independent predictive potential of heart rate reduction-2 for HFrecEF was examined by multivariate logistic regression analysis. As a result, heart rate reduction-2 was a powerful predictor of HFrecEF, independently of several confounding factors including the absence of ischemic heart disease and baseline LVDd (Table 5). In particular, the odds ratio for predicting HFrecEF in the

Table 3. Comparison of treatment during follow-up and clinical findings and medications at the end of follow-up between the 2 groups

	Persistent HFrEF (n = 46)	HFrecEF (n = 64)	P-value
Invasive treatment and device therapy during follow-up			
PCI	20%	19%	0.916
CABG	2%	0%	0.240
Valve surgery	0%	0%	1.000
Pacemaker implantation	4%	2%	0.381
ICD implantation	4%	3%	0.738
CRT	7%	5%	0.679
Catheter ablation	9%	8%	0.869
ECG and UCG findings (at the end of follow-up)			
Heart rhythm (atrial fibrillation)	12%	22%	0.177
Heart rate [bpm]	79 ± 18	72 ± 14	0.013
CLBBB	19%	5%	0.115
QRS duration [msec]	123 ± 28	105 ± 24	< 0.001
LVEF [%]	29.9 ± 5.1	52.6 ± 7.4	< 0.001
LVDd [mm]	60.2 ± 7.1	49.9 ± 6.4	< 0.001
LVDs [mm]	51.5 ± 8.1	35.4 ± 6.7	< 0.001
LA diameter [mm]	43.4 ± 7.3	38.9 ± 7.5	0.002
IVC diameter [mm]	13.4 ± 5.0	13.3 ± 3.9	0.940
Physical and laboratory findings and medications (just before UCG examination)			
Systolic blood pressure [mmHg]	125 ± 18	129 ± 22	0.298
Diastolic blood pressure [mmHg]	73 ± 12	74 ± 14	0.667
Heart rate [bpm]	83 ± 13	76 ± 11	0.006
Creatinine [mg/dL]	1.20 ± 1.02	1.01 ± 0.42	0.175
eGFR [mL/min/1.73 m^2]	59.3 ± 26.5	61.6 ± 21.8	0.619
BNP [pg/mL]	384 ± 411	68 ± 78	< 0.001
β-blocker	84%	91%	0.584
β-blocker dose [mg/day*]	8.0 ± 5.3	8.8 ± 4.9	0.457
RAS inhibitor	57%	72%	0.107
MR antagonist	57%	55%	0.829
Loop diuretic	75%	63%	0.176
Digitalis	9%	2%	0.068
Amiodarone	25%	16%	0.230

Values are mean ± SD or percentage. BNP — brain natriuretic peptide; CABG — coronary artery bypass grafting; CLBBB — complete left bundle branch block; CRT — cardiac resynchronization therapy; ECG — electrocardiography; eGFR — estimated glomerular filtration rate; HFrEF — heart failure with reduced ejection fraction; HFrecEF — heart failure with recovered ejection fraction; ICD — implantable cardioverter defibrillator; IVC — inferior vena cava; LA — left atrial; LVDd — left ventricular diameter at end-diastole; LVDs — left ventricular diameter at end-systole; LVEF — left ventricular ejection fraction; MR — mineralocorticoid receptor; PCI — percutaneous coronary intervention; RAS — renin-angiotensin system; UCG — ultrasound echocardiography; *Carvedilol equivalent dose; i.e., bisoprolol 5 mg was considered equivalent to carvedilol 20 mg

group with heart rate reduction-2 of ≥ 19.5 bpm (vs. < 19.5 bpm) was very high at 8.55 ($p < 0.001$). The significance of heart rate reduction-2 for predicting HFrecEF was maintained even when reanalyzed only in patients without tachyarrhythmia as a cause of heart failure [odds ratio (per 1 bpm) 1.04; 95% confidence interval 1.01–1.09, $p = 0.006$].

Discussion

Some previous studies indicated that baseline heart rate at the index heart failure hospitalization was significantly higher in patients with HFrecEF than in those with persistent HFrEF [5, 7, 8]. Of these previous studies, the report by Park et al. [7]

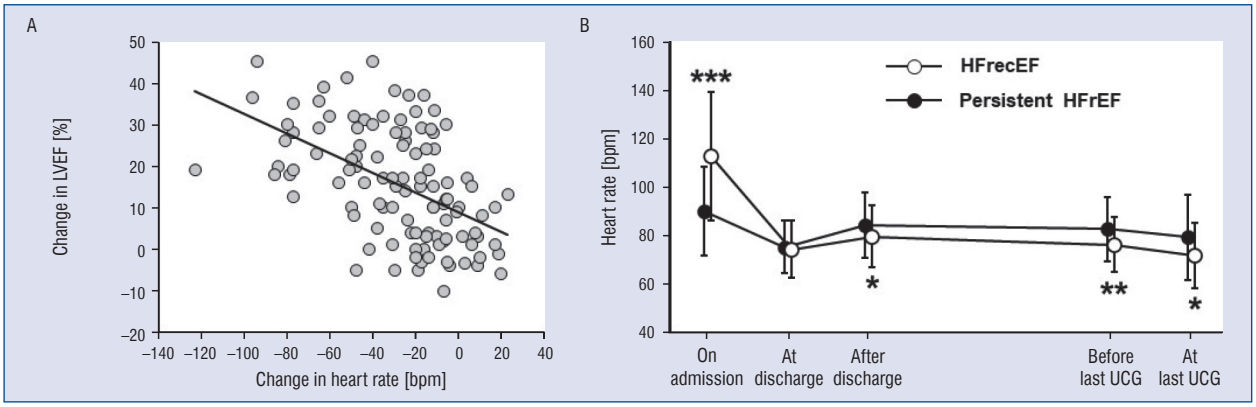

Figure 2. A. Correlation between respective changes in heart rate and left ventricular ejection fraction (LVEF) through the follow-up period (from the time of admission of the index heart failure hospitalization) in the overall subjects. The change in heart rate was significantly correlated with the change in LVEF ($r = –0.508$, $p < 0.001$). **B.** Changes in heart rate over time throughout the follow-up period in patients with persistent heart failure with reduced ejection fraction (HFrEF) and heart failure with recovered ejection fraction (HFrecEF). Represented heart rates are at the time of admission of the index hospitalization (on admission), at the time of discharge (at discharge), at the first outpatient visit after discharge (after discharge), at the outpatient visit just before the last ultrasound echocardiography (UCG) examination (before last UCG), and at the end of follow-up, i.e., at the last UCG examination (at last UCG). Values are given as mean ± SD. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ vs. persistent HFrEF

Table 4. Association of heart rhythm and heart rate on hospital admission for heart failure and early-phase heart rate reduction with HFrecEF by univariate and multivariate logistic regression analysis

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
AF on admission, yes	2.80 (1.22–6.84)	0.015	0.70 (0.22–2.14)	0.535
Heart rate on admission, 1 bpm	1.04 (1.02–1.07)	< 0.001	0.99 (0.94–1.03)	0.594
Heart rate reduction-1, 1 bpm	1.05 (1.03–1.08)	< 0.001	1.02 (0.97–1.07)	0.416
Heart rate reduction-2, 1 bpm	1.06 (1.03–1.08)	< 0.001	1.05 (1.01–1.10)	0.007

AF — atrial fibrillation; CI — confidence interval; HFrecEF — heart failure with recovered ejection fraction; OR — odds ratio. Heart rate reduction-1 indicates heart rate on admission minus at discharge. Heart rate reduction-2 indicates heart rate on admission minus heart rate at the first outpatient visit after discharge

Table 5. Predictive value of early-phase heart rate reduction for HFrecEF by multivariate logistic regression analysis

	Multivariate analysis (1)		Multivariate analysis (2)	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age, 1 year	1.00 (0.95–1.05)	0.939	1.00 (0.95–1.05)	0.906
Gender, men	3.34 (0.93–12.7)	0.064	3.72 (1.02–14.8)	0.046
Ischemic heart disease, yes	0.08 (0.02–0.28)	< 0.001	0.08 (0.02–0.26)	< 0.001
Baseline LVEF, 1%	1.06 (0.96–1.17)	0.270	1.05 (0.95–1.15)	0.362
Baseline LVDd, 1mm	0.89 (0.80–0.98)	0.018	0.87 (0.79–0.96)	0.005
Heart rate reduction-2, 1 bpm	1.05 (1.02–1.07)	< 0.001		
Heart rate reduction-2 ≥ 19.5 bpm, yes			8.55 (2.92–28.7)	< 0.001

CI — confidence interval; HFrecEF — heart failure with recovered ejection fraction; LVDd — left ventricular diameter at end-diastole; LVEF — left ventricular ejection fraction; OR — odds ratio. Heart rate reduction-2 indicates heart rate on admission minus at the first outpatient visit after discharge

showed that increased heart rate at baseline was one of the independent predictors of HFrecEF. To our knowledge, however, there have been no studies examining the involvement of change in heart rate in the early phase of heart failure onset in the improvement of cardiac function and the prediction of heart failure phenotypes. In our study, the reduction of heart rate in the early phase after the onset of heart failure rather than the increased heart rate on hospital admission was more significantly associated with HFrecEF. Our multivariate logistic regression revealed that the greater heart rate reduction from the time of heart failure admission to the first outpatient visit after discharge was a powerful predictor of HFrecEF, independently of several confounding factors such as ischemic heart disease and baseline LVDd. Thus, this study was the first to demonstrate that early-phase heart rate reduction after heart failure onset is an independent predictor of the subsequent recovery of LVEF in HFrEF patients.

First we obtained the findings that the reduction of heart rate through the observation periods (i.e., from the time of hospital admission for heart failure to the end of follow-up) was closely correlated with the improvement of LVEF in patients initially diagnosed with HFrEF, as shown in Fig. 2A. Similar findings were shown in the previous study by Flannery et al. [16]. Their analysis using 26 clinical trials of β-blockers in heart failure patients with systolic dysfunction clearly indicated that the improvement of LVEF after treatment with β-blockers (a mean follow-up duration of 9.6 months) was strongly correlated with the magnitude of heart rate reduction. However, the findings that there was a close correlation between lowered heart rate and improved LVEF did not clarify a causal relationship between them, because the possibility was also considered that the decrease in heart rate and the recovery of left ventricular contractility might have progressed in parallel during the course of heart failure treatment including drug therapy. We therefore investigated changes in heart rate over time by selecting several key points through the follow-up periods in both groups with HFrecEF and persistent HFrEF. As a result, a greater reduction of heart rate in the early phase of the course of heart failure therapy was observed in patients with HFrecEF, and the levels of heart rate in the HFrecEF group during follow-up after discharge were continuously lower than those in the persistent HFrEF group. The findings indicated that heart rate reduction in the HFrecEF group preceded the recovery of LVEF, surely suggesting that early-phase heart rate reduction was a predictor of LVEF improvement in patients with HFrEF. Because there was no difference in the percentages of β-blocker use or its doses at discharge of heart failure hospitalization and the end of follow-up between the 2 groups with HFrecEF and persistent HFrEF, it is unlikely that underdosing of β-blockers led to less heart rate reduction in the persistent HFrEF group compared with the HFrecEF group.

β-blocker therapy is well known to contribute to ventricular reverse remodeling and reduced mortality in heart failure patients with systolic dysfunction [14–17], and it may be plausible to assume that this favorable effect is mediated by the inhibition of sympathetic nerve activity. However, the findings by Flannery et al. [16], that both improved LVEF and decreased relative risk in all-cause mortality with β-blockers were closely associated with the extent of heart rate reduction in HFrEF patients, suggest that a major contributor to the clinical benefits of β-blocker therapy in heart failure with systolic dysfunction may be the heart rate-lowering effect of the agent. In addition, isolated heart rate reduction with ivabradine, which inhibits the I_f current but has no other known direct effects on the myocardium or blood vessels [25], is shown to have beneficial effects on both reversing ventricular remodeling and improving cardiovascular prognosis in HFrEF patients [11,18–21]. These studies suggest that heart rate itself, apart from sympathetic nerve activity, is significantly involved in cardiovascular outcomes including cardiac structural and functional changes in HFrEF. Therefore, heart rate is a risk marker in heart failure patients with systolic dysfunction, as shown in our study, but it may be also a risk factor and therapeutic target for heart failure.

In the present study, the rate of subjects with atrial fibrillation rhythm on hospital admission for heart failure was significantly higher in the HFrecEF group than in the persistent HFrEF group. There have been contradictory findings on how concomitant atrial fibrillation is associated with the improvement of LVEF in patients with HFrEF [5, 6, 9], and some previous studies indicated that coexisting atrial fibrillation was a predictor of improved LVEF [5, 6]. However, the involvement of heart rate (or tachycardia) was not considered in the studies showing the positive association of higher frequency of atrial fibrillation with HFrecEF. Because our logistic regression analysis showed that early-phase heart rate

reduction rather than atrial fibrillation rhythm and heart rate on admission was significantly associated with HFrecEF, it is unlikely that atrial fibrillation itself is positively related to the subsequent improvement of LVEF in HFrEF patients. From another perspective, it is conceivable that the restoration of sinus rhythm (obviously accompanied by a decrease in heart rate) in patients with atrial tachyarrhythmias, which were more common in the HFrecEF group, may have contributed to the subsequent improvement in LVEF.

There are several limitations in this study. The present findings were derived from retrospective longitudinal observations carried out in a single center with a relatively small sample size. The decision about therapeutic strategies for heart failure including medications and invasive treatment was left to each physician's discretion. In addition, the timing of repeat echocardiographic examinations was also left to the discretion of the attending physician, but not at pre-specified interval, suggesting that serial echocardiograms available for analyses might have been influenced by the patients' clinical status. Conversely, it can be a strength of our study that patients with a transient LVEF ≥ 40% (fluctuating LVEF) and with an absolute LVEF increase < 10 points were excluded to clearly distinguish the 2 groups with persistent HFrEF and HFrecEF.

Conclusions

The present study demonstrated that heart rate reduction in the early phase after heart failure onset was a powerful independent predictor of the subsequent recovery of LVEF in HFrEF patients. This conclusion should be confirmed in a future prospective study. An additional study is also needed to investigate whether further reduction of heart rate with increased doses of β-blockers and by ivabradine administration can contribute to subsequent amelioration of LVEF in patients such as those diagnosed with persistent HFrEF in this study.

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