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Cardiomyopathy and Heart Failure

Effect of Heart Rate-Oriented Therapy on Diastolic Functions in Patients with Heart Failure with Reduced Ejection Fraction

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Background: Resting heart rate (HR) is a strong predictor of cardiovascular mortality and morbidity in patients with heart failure with reduced ejection fraction (HFrEF). However, the effects of HR-lowering therapy on diastolic function in HFrEF patients are not well described. In this study, we aimed to investigate the effect of lowering HR on diastolic function in HFrEF patients with sinus rhythm.

Methods: Fifty patients with HFrEF with coexisting diastolic dysfunction and sinus rhythm with resting HR > 70 bpm were prospectively included in the study. All patients were treated with intended HR-lowering therapy, which targeted a HR below 70 bpm. We divided the whole population according to the resting HR achieved with strict rate control (group 1) and to that achieved without strict rate control (group 2; HR > 70 bpm) at the end of the study. Left ventricular diastolic function and B-type natriuretic peptide (BNP) values at baseline and at the end of the study were compared in both groups.

Results: No significant differences were found between the groups in terms of baseline parameters except for lower diastolic blood pressure in group 2. At the end of follow-up, E/Em ratio, E/A ratio and left atrial area significantly decreased with an increased deceleration time in group 1. The changes in HR (delta HR) were correlated with E/Em ($r = 0.67$, $p < 0.001$) and delta BNP level ($r = 0.49$, $p < 0.001$).

Conclusions: This study showed that an effective HR lowering in patients with HFrEF can lead to improvements in diastolic function.

Key Words: Brain natriuretic peptide • Diastolic dysfunction • Heart failure • Heart rate

INTRODUCTION

Resting heart rate (HR) is a strong predictor of cardiovascular mortality and morbidity in the general population as well as in patients with hypertension, coronary artery disease and chronic heart failure.[1-5] Readmission for heart failure (HF) is also a predictor of cardiovascular mortality. A recent study showed that HF patients who suffered from 30-day readmission had a worse prognosis at 6 months of follow-up.[6] In patients with heart failure with reduced ejection fraction (HFrEF), a higher HR is a general finding that attenuates the decrease in cardiac output or preserves cardiac output at the cost of impaired left ventricular (LV) filling, increased myocardial O2 consumption and reduced coronary perfusion time. In the last decade, increasing clinical evidence has indicated the beneficial effects of HR-lowering therapies on clinical outcomes in HFrEF patients.[7-11] The clinical benefits of this therapy has been attributed to improvements in systolic function and symptoms, reverse remodeling of ventricular size, delayed progression of HF, and reduction of arrhythmic events, particu-

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larly for treatment with beta blockers.[12,13] The TSOC-HFrEF registry showed evidence of suboptimal practice of guideline-directed medical therapy and a high HF re-hospitalization rate in Taiwan. Ultimately, their data indicated the need for further improvements in HF care.[14]

Some small studies have demonstrated that treatment with beta blockers can also lead to an improvement in diastolic function in HFrEF patients.[15,16] A recent clinical study on ivabradine also indicated an improvement in diastolic function in patients with HF with diastolic dysfunction.[17] As HFrEF is usually characterized by alterations in LV filling, and as patients with Doppler evidence of restrictive or pseudonormal diastolic filling pattern have poor prognosis and clinical outcomes, treating diastolic dysfunction should also be a focus of therapy.[18,19] A continuous direct association has been reported between resting HR and clinical outcomes,[20] however whether such a relationship exists between diastolic dysfunction and resting HR has yet to be elucidated. In addition, limited data are available on the association between resting HR and diastolic dysfunction in patients with HFrEF. In this study, we aimed to evaluate the effects of HR-oriented therapy on diastolic function in patients with HFrEF.

MATERIAL AND METHODS

Study population and protocol

All consecutive patients admitted with HFrEF (symptoms and LV ejection fraction < 40% according to the 2016 ESC guidelines for the diagnosis and treatment of acute and chronic HF) with coexisting diastolic dysfunction (symptoms and an echocardiographic pseudonormal pattern according to the 2016 European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic HF) and sinus rhythm with a resting HR > 70 bpm between July 2013 and February 2014 were prospectively screened for the study.[21] Patients with atrial fibrillation (n = 29), pacemaker rhythm or cardiac resynchronization therapy (CRT) (n = 9), New York Heart Association functional class IV or ongoing clinical decompensation (n = 14), and severe renal and/or hepatic insufficiency (n = 14) were excluded. Consequently, of the 150 HFrEF patients, 84 were eligible for enrolment in this study. After the patients provided written informed consent, resting electrocardiography (ECG), baseline transthoracic echocardiography (TTE) and B-type natriuretic peptide (BNP) evaluations were conducted to obtain the baseline measurements. The patients' medical therapy was adjusted according to these baseline evaluations, targeting a resting HR of < 70 bpm. The dosages of beta blockers were 10 mg o.d. for nebivolol, 12.5 mg b.i.d. for carvedilol, 5 mg o.d. for bisoprolol and 200 mg o.d. for metoprolol succinate; these are described as the target doses in the 2016 ESC guidelines for the diagnosis and treatment of acute and chronic HF. The patients were followed up monthly with ECG and clinical assessments until the end of the sixth month. According to the resting HR obtained from these clinical visits, negative chronotropic drugs were either uptitrated or added according to the baseline status of the medications used. For the HR-oriented therapy, beta blockers were used as the first-line therapy, ivabradine as the second-line therapy and digitalis as the third-line therapy. Other medical therapies including diuretics, renin-angiotensin system blockers and other antihypertensives were not altered by the monitoring physician during the entire follow-up period. The patients who required discontinuation of these therapies during the follow-up period were also excluded from the study. Among the 84 patients enrolled in the study, 26 were excluded because of this reason. Two patients underwent CRT implantation and sixdied during the follow-up period. The remaining 50 patients completed the 6-month follow-up period. At the end of the sixth month, final evaluations including resting HR, BNP and TTE were performed. At the end of the follow-up period, 23 patients had not achieved the target HR despite the HR-oriented therapy due to intolerance to the first-, second- and third-line treatments. Intolerance to these treatments was definedas presenting with clinical manifestations including bradycardia, hypotension, arrhythmias, hypothermia, hypoglycemia, seizures and QT prolongation. We then subclassified the whole population according to the average resting HR obtained: group 1 with strict rate control ≤ 70 bpm (n = 27); and group 2 without strict rate control > 70 bpm (n = 23). The laboratory and echocardiographic parameters at baseline and at the end of the study were compared in both groups.

Measurements

All patients underwent detailed TTE examination us-

ing a Philips HD 11 XE system and a 2.5-3.5 MHz transducer. Routine echocardiographic evaluations were conducted focusing on the Doppler and tissue Doppler (TD) parameters of the LV, by the same experienced echocardiographer. The LV diameter, LV volume, interventricular septum thickness, left atrial diameter and left atrial area (LAA) were determined according to the guidelines of the American Society of Echocardiography.[22] The LV ejection fraction (LVEF) was estimated using the modified Simpson method.[23] Pulsed Doppler transmitral inflow velocities, including early-diastolic peak-flow velocity (E), late-diastolic flow velocity (A), their ratio (E/A) and deceleration time (DT), were obtained. Early diastolic mitral annular velocity (e') and left ventricular peak systolic myocardial velocity (LV Sm) were recorded for each patient through TD imaging of the septal wall of the LV.[24] The parameters necessary to calculate the Tei index were obtained by TD in the apical four-chamber view. The isovolumetric contraction time (IVCT), isovolumetric relaxation time (IVRT) and ejection time (ET) were measured from the TD tracings of the mitral annulus. The Tei index was calculated according to the formula: Tei index = (IVCT + IVRT)/ET for each ventricle.[25] Systolic pulmonary artery pressure (SPAP) was measured according to the tricuspid regurgitant jet velocity using the Bernoulli equation and the estimated right atrial pressure.[26]

Blood samples for BNP levels were drawn in the morning from fasting and supine patients. The plasma BNP level was determined immunoenzymatically using an AxSYM kit (Abbott). The reference range of the plasma BNP levels determined using quantitative Abbott immunoenzymatic kits was 0.00-100.00 pg/mL. The resting HR was measured by 12-lead electrocardiography after 2-3 minutes of rest in the supine position.

Statistical analysis

SPSS statistical software (version 15.0 for Windows, SPSS Inc., Chicago, IL, USA) was used for all statistical calculations. Continuous variables were presented as the mean ± standard deviation (SD), BNP was presented as the median, and categorical variables were presented as percentages. Comparisons among the different data for each patient at different time points of assessment were performed using the two-tailed paired Student's *t* test. The delta values for the parameters were calculated in each group according to the difference between the final and the baseline values. Comparisons of the delta values in each group were performed using the independent sample Student's *t* test. Categorical variables between the two subgroups were compared using the chi-square test. Spearman correlation analysis was used to evaluate the associations among the parameters. Statistical significance was defined as $p < 0.05$.

RESULTS

Fifty patients completed the entire 6-month follow-up period. The mean age of the study population was 67.2 ± 11.3 years, with a male predominance (73.9%). The mean LVEF was 28%, and the etiology of the HFrEF was ischemic heart disease in 73.9% of the patients. At the end of the 6-month follow-up period, 27 patients achieved the target resting HR (group 1). In this group, the resting HR decreased from 84.4 to 62.5 bpm. In the remaining 23 patients (group 2), the resting HR did not change significantly at the end of the study (89.5 bpm vs. 84.9 bpm; p = 0.110). The main reason for the ineffective rate control in group 2 was side effects of the used drugs, which limited the necessary uptitration. Among these side effects, hypotension was the most common, as it limited the ideal uptitration of the beta blockers. The baseline clinical and laboratory characteristics of the groups are outlined in Table 1. No significant differences were found among the baseline parameters of the two groups except for diastolic blood pressure and diuretic usage. Baseline diastolic blood pressure was significantly lower (66.5 ± 10.4 mmHg vs. 70.9 ± 7.5 mmHg; p = 0.04) and diuretic usage was slightly more frequent in group 2 than in group 1 (95.7% vs. 74.1%; p = 0.04). The baseline median BNP values were similar in group 1 and group 2 (p = 0.76). The median baseline BNP value for group 1 was 363 pg/ml [interquartile range (IQR): 90-918 pg/ml] and the median baseline BNP value for group 2 was 360 pg/ml (IQR: 219-887 pg/ml).

The final changes in the laboratory and echocardiographic parameters according to the baseline values are summarized for both groups in Table 2. In group 1, the BNP, ratio of transmitral E velocity to early diastolic mitral annular velocity (E/e'), E/A and LAA significantly decreased, whereas DT significantly increased at the end

Table 1. Comparison of baseline demographical, clinical and laboratory parameters between study groups

	Group 1 (n = 27) Achieved HR < 70 bpm	Group 2 (n = 23) Achieved HR ≥ 70 bpm	p value
Age, years	65.7 ± 13.7	69.5 ± 7.9	0.25
Male, n (%)	20 (74%)	17 (74%)	0.99
Functional class, n (%)			0.36
NYHA II	6 (22%)	8 (35%)	
NYHA III	21 (78%)	15 (65%)	
Aetiology, n (%)			0.40
Ischemic	17 (63%)	17 (74%)	
Non-ischemic	10 (37%)	6 (26%)	
DM, n (%)	9 (33%)	11 (48%)	0.29
HT, n (%)	16 (59%)	13 (56.5%)	0.84
CKD, n (%)	2 (7%)	2 (9%)	0.86
Smoking, n (%)	5 (20%)	3 (23%)	0.56
Baseline medication			
ACEI/ARB, n (%)	23 (85%)	20 (87%)	0.85
Loop diuretics, n (%)	20 (74%)	22 (96%)	0.04
Aldosterone ant. n (%)	19 (70%)	19 (83%)	0.31
Baseline HR, bpm*	85.4 ± 12.4	89.5 ± 9.1	0.06
Systolic-BP, mmHg*	129.4 ± 17.8	120 ± 22.6	0.10
Diastolic-BP, mmHg*	70.9 ± 7.5	66.5 ± 10.4	0.04
E/Em*	15.8 ± 5.7	15.5 ± 5.3	0.95
LAA, cm^2*	25.5 ± 5.4	25.4 ± 6.5	0.80
BNP, pg/ml#	363 (IQR: 90-918)	360 (IQR: 219-887)	0.76

* Mean ± SD. # Median.

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BNP, brain-type natriuretic peptide; BP, blood pressure; CKD, chronic kidney disease; DM, diabetes mellitus; E/Em, ratio of transmitral E velocity to early diastolic mitral annular velocity; HR, heart rate; HT, hypertension; IQR, interquartile range; LAA, left atrial area; NYHA, New York Heart Association.

Table 2. Comparison of basal and post-follow-up echocardiographic data and BNP values of group 1 and group 2

	Group 1 (n = 27)			Group 2 (n = 23)		
	Initial	Post follow-up	p value	Initial	Post follow-up	p value
HR*	85.4 ± 12.4	62.8 ± 4.9	0.000	89.5 ± 9.1	84.9 ± 11.1	0.110
BNP (pg/mL)#	363 (IQR: 90-918)	202 (IQR: 66-403)	0.002	360 (IQR: 219-887)	242 (IQR:124-939)	0.020
E/Em*	15.8 ± 5.6	12.5 ± 5.9	0.010	15.5 ± 5.2	17.7 ± 10.7	0.500
E/A *	1.6 ± 0.8	1.1 ± 0.6	0.023	1.5 ± 0.8	1.6 ± 1.6	0.800
DT (ms)*	140.8 ± 24.7	161 ± 47.9	0.040	145.3 ± 40.2	147.7 ± 48.1	0.980
LAA (cm^2)*	25.5 ± 5.4	23.3 ± 5.2	0.010	25.4 ± 6.7	24.1 ± 4.9	0.330
IVRT*	143.2 ± 33.0	133.1 ± 27.1	0.130	125.0 ± 28.5	143.8 ± 46.0	0.170
Vp*	36.1 ± 8.5	36.1 ± 6.7	0.750	37.0 ± 7.7	35.2 ± 5.0	0.310
LVEF*	28.5 ± 6.7	29.7 ± 5.6	0.420	29.2 ± 4.6	30.3 ± 6.2	0.210
LV Sm*	6.6 ± 1.7	7.0 ± 1.7	0.350	6.9 ± 1.9	6.2 ± 1.6	0.110

* Mean ± SD. # Median.

BNP, brain-type natriuretic peptide; DT, deceleration time; E/A, ratio of transmitral early-diastolic peak-flow velocity to late diastolic flow velocity; E/Em, ratio of transmitral E velocity to early diastolic mitral annular velocity; HR, heart rate, IQR, interquartile range; IVRT, isovolumetric relaxation time; LAA, left atrial area; LVEF, left ventricular ejection fraction; LV Sm, left ventricular peak systolic myocardial velocity; Vp, transmitral flow propagation velocity.

of the follow-up (Table 2). The final median BNP and the baseline median BNP values were compared for each group. In group 1, the final median BNP value was 202 pg/ml (IQR: 66-403 pg/ml) with a significant difference from baseline (p = 0.002). In group 2, the final median BNP value was 242 pg/ml (IQR: 124-939 pg/ml), also with a significant difference from baseline (p = 0.02) (Table 2). In group 2, no significant changes were found in

any of the echocardiographic parameters.

The delta values for resting HR, E/Em and BNP were also assessed in each group to calculate differences between the baseline values and the final values. Spearman correlation analysis was performed to analyze the correlations of these delta parameters (Table 3). This analysis demonstrated a strong correlation between delta HR and delta E/Em ($r = 0.675$; $p < 0.001$), a moderate correlation between delta HR and log delta BNP ($r = 0.499$; $p < 0.001$) and a weak correlation between log delta BNP and delta E/Em ($r = 0.266$; $p = 0.107$).

When the final negative chronotropic medications were compared between the groups, no differences were found in beta blockers and ivabradine usage. Beta blockers were used in all of the patients in both groups. We did not perform a comparative analysis on the mean dosages of beta blockers between the groups because the type of beta blocker was not uniform among patients. Thus, dividing the groups into metoprolol, carvedilol, nebivolol and bisoprolol subgroups did not allow us to conduct a meaningful analysis because of the small number of patients in these groups. However, the beta blocker dosages were clearly lower in group 2, as they could not tolerate the optimal uptitration mainly because of symptomatic hypotension. For ivabradine usage, the frequencies were similar between the groups by the end of the follow-up. As expected, the mean dosage of ivabradine in group 2 was significantly higher than that in group 1 (13.8 mg/day vs. 11.5 mg/day; $p = 0.023$).

Table 3. Correlation between the decrease in HR and decreases in E/Em and BNP values at the end of follow-up

Dual correlations	r	p value
ΔHR – ΔE/Em	0.675	< 0.001
ΔHR – log (ΔBNP)	0.499	< 0.001
ΔE/Em – log (ΔBNP)	0.266	0.107

BNP, brain-type natriuretic peptide; E/Em, ratio of transmitral E velocity to early diastolic mitral annular velocity; HR, heart rate.

DISCUSSION

This study showed that effective HR lowering led to improvements in diastolic dysfunction compared with lenient HR control in patients with HFrEF and sinus rhythm. In our analysis, a direct association was found between the HR achieved after 6 months of treatment and the improvement in diastolic function parameters. This finding suggests that HR reduction has a direct therapeutic role in diastolic dysfunction. In HF, this finding is consistent with the pathophysiological notion that reducing HR decreases energy expenditure, increases blood supply by prolonging diastole, and improves in vivo and in vitro force-frequency associations.[27-29] Furthermore, HR is directly related to vascular elastance and ventricular loading.[30] Therefore, HR reduction unloads the ventricle, and the effect is greatest in diseased hearts. Despite these benefits of HR reduction, the recommendations of the current heart failure guidelines on reducing HR are conflicting. In the 2012 ESC heart failure guidelines, a target HR of 70/min was recommended for the first time. For patients who could not achieve the target HR despite well tolerating the beta blocker dosage, ivabradine was recommended with a class 2a indication. For patients intolerant to beta blockers,ivabradine was recommended with a class 2b indication if the HR was above 70/min.[31] A recent study demonstrated that adding ivabradine to the standard therapy reduced HR and significantly improved LV asynchrony and Tei index in systolic HF patients.[32] However, in the 2013 ACC/AHA heart failure guidelines, no target HR was recommended, and beta blockers were recommended on a dose basis rather than on an HR basis. Evidence-based target doses of beta blockers were recommended for every patient if they could tolerate them well. Ivabradine usage was not recommended in these guidelines.[33] Therefore, targeting a certain HR among HFrEF patients remains a question for clinicians.

As the co-existence of systolic and diastolic dysfunction is common among HFrEF patients, improving diastolic dysfunction should be an important therapeutic focus. Moreover, HFrEF patients with diastolic dysfunction are more symptomatic and have a poorer prognosis than those with normal diastolic function.[18,19] Therefore, treating diastolic dysfunction in HFrEF patients may provide symptom relief and improve their prognosis.

To the best of our knowledge, this study is the first to investigate the role of HR reduction in diastolic function in HFrEF patients. The benefits of HR reduction in HFrEF patients were demonstrated in clinical outcomes and in left ventricular remodelling.[11,12] The strongest

evidence was based on the results of HFrEF treatment with the Systolic Heart Treatment with the If Inhibitor Ivabradine Trial (SHIFT) study, which is the largest trial on ivabradine to date. In the SHIFT trial, hospital admission for worsening HF and death due to HF was significantly reduced by ivabradine compared with a placebo.[11] An echocardiographic substudy of the SHIFT trial demonstrated the negative remodeling effects of ivabradine on the left ventricle. Patients receiving ivabradine were shown to have a significant reduction in left ventricular systolic and diastolic volumes.[12] As ivabradine does not have inotropic or direct vasodilating effects and reduces HR by a direct effect on the sinoatrial node, the effects of ivabradine treatment were primarily attributed to the reduction in HR. However, in these trials, the effect of ivabradine on diastolic function was not evaluated. Subsequently, some animal studies demonstrated the beneficial effects of ivabradine on diastolic function.[34] Recently, this effect was shown in a clinical trial, in which only patients with HF alone with preserved ejection fraction were enrolled.[17]

Beta blockers are another class of negative chronotropic drug used in HFrEF patients. Several large trials have demonstrated the benefits of these drugs in cardiovascular outcomes and even in mortality.[1-5] Some small studies have shown beta blockers to be effective in improving diastolic dysfunction in HFrEF patients.[14,16] However, in these trials, the improvement in diastolic function was found to be independent of HR reduction and was attributed solely to the effects of the drugs. Beta blockers are considered to improve diastolic dysfunction through reducing oxygen consumption and cardiac work, vascular peripheral dilatation, metabolic effects leading to the reduction of myocardial fibrosis and LV chamber rigidity, restoration of Ca^{2+} homeostasis, and improved active relaxation.[35,36]

Although all of the studies mentioned above demonstrated the benefits of HR-lowering therapies in HFrEF patients, the focus of the trials was always on the drugs rather than HR. Our trial is the first to focus on the effects of HR reduction on diastolic function in HFrEF patients. Our results indicate that effectively lowering HR improves diastolic function more effectively than lenient HR control in patients with HFrEF. The better the diastolic function, the better the LV unloading. In our study population, a reduction in BNP was more prominent in group 1 than in group 2, in parallel with the improvements in diastolic function. The diuretic and vasodilator therapies of the patients were not changed during the entire study period. We observed that the study patients complied better with a low-sodium diet and with the medications under the close follow-up of the study, and that they had a better volume status at the end of the study.

Although each patient was intended to be treated to achieve the target HR, the HR of some patients was not effectively reduced despite the treatment (group 2: n = 23). The differences in the final parameters could be related to the different baseline hemodynamic profiles of the groups. However, in comparing the baseline clinical and laboratory profiles of the groups, no differences were found between them except for baseline diastolic BP, which was significantly lower in group 2 than in group 1 (66.5 $\pm$ 10.4 mmHg vs.70.9 $\pm$ 7.5 mmHg; $p = 0.04$). This difference maybe the main reason for the limitation of beta blocker uptitration and for the ineffective HR reduction in group 2. We also demonstrated associations among HR reduction, diastolic dysfunction and LV unloading through correlation analyses. We showed that delta HR was strongly correlated with delta E/Em and moderately correlated with delta BNP ($r = 0.675$; $p < 0.001$ and $r = 0.476$; $p < 0.001$, respectively).

A recent study on ivabradine also demonstrated the effectiveness of ivabradine in left ventricular unloading.[30] However, in this study, diastolic function was not evaluated, and this effect was attributed to improvements in vascular elastance and ventriculoarterial coupling.

Study limitations

Our study has some limitations. The small population of the study group undoubtedly limited the study. Although the results achieved statistical significance, they must be considered carefully, and further investigations are needed to confirm our results. The LV diastolic function was assessed noninvasively using Doppler echocardiography. Although this method is widely applied, it is not the gold standard as the majority of the parameters are affected by the volume status of the patient. The volume status of the patients could not be fully controlled even if we did not make any changes in the diuretic and vasodilator therapies of the patients during the entire study period. Any change in volume status of

the patient secondary to dietary factors could have contributed to the results. As our trial was not a specific drug trial, the distribution of the types and dosages of the negative inotropic drugs were not uniform among the patients. This may also have contributed to the findings and limited the ruling out of the drug effects on the results.

CONCLUSIONS

The results of this study, together with previous literature, suggest the beneficial effects of strict HR lowering on diastolic function in patients with HFREF. This effect may contribute to LV unloading, thus resulting in the relief of symptoms and better prognosis. HR-oriented therapy should be provided to all HFrEF patients with a target HR of < 70 bpm.

AUTHOR DISCLOSURE AND CONFLICT OF INTEREST

All of the authors have no conflicts of interest or financialties to disclose.

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