RAPID COMMUNICATION

Effect of Ivabradine on Left Ventricular Diastolic Function of Patients With Preserved Ejection Fraction
— Results of the IVA-PEF Study —

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Background: The association between heart rate (HR) reductions caused by ivabradine and left ventricular (LV) diastolic function in heart failure with preserved ejection fraction (HFpEF) remains uncertain because of off-label use. Thus, the present study investigated the effect of HR reductions by ivabradine on LV diastolic function in HFpEF patients.

Methods and Results: This study enrolled 16 HFpEF patients with HR ≥75 beats/min. After 3 months administration of ivabradine, no significant changes were observed in mitral inflow E and mitral e' annular velocities, B-type natriuretic peptide, or left atrial volume index, but there were significant improvements in global longitudinal strain.

Conclusions: Ivabradine did not improve LV diastolic function for HFpEF patients with HR ≥75 beats/min. Because this may be due to some study limitations, further studies should be conducted.

Key Words: Heart rate; Ivabradine; Left ventricular diastolic function

The detrimental effects of elevated heart rate (HR) on patients with either heart failure (HF) with reduced ejection fraction (HFrEF) or HF with preserved ejection fraction (HFpEF) are well documented. Increased HR is also an independent risk factor for cardiovascular mortality and morbidity, even for subjects without overt cardiovascular diseases who have risk factors for HF such as hypertension, impaired glucose metabolism, obesity, and diabetes.[1,2] Beta-blockers have demonstrated efficacy in improving the morbidity and mortality of patients with HFrEF by reducing HR, thus reducing myocardial oxygen demand or consumption and improving left ventricular (LV) filling and coronary perfusion.

Ivabradine, a selective sinus node I_f channel inhibitor, belongs to a new class of HR-lowering drugs that reduce HR without affecting inotropy, diastology, blood pressure, or vascular resistance, and its efficacy and safety for patients with HFrEF has been widely demonstrated.[3,4] However, the association between HR or HR reduction and LV diastolic function in HFpEF patients remains uncertain. Moreover, ivabradine for HFpEF patients is currently restricted to off-label use. Thus, we designed the present multicenter, prospective, uncontrolled, open-label, single-assignment, and single-arm interventional study to investigate the effects of HR reductions by ivabradine on LV diastolic function in HFpEF patients. This study was specified as clinical research in the Japanese context.

Methods

The Effect of Ivabradine on Left Ventricular Diastolic Function in Patients With Preserved Ejection Fraction (IVA-PEF) was a multicenter, prospective, uncontrolled, open-label, single-assignment, and single-arm interventional study examining the effects of ivabradine on LV diastolic function in HFpEF patients. The design and protocol of IVA-PEF have been reported previously.[5] Briefly, to be eligible for inclusion in the study, patients had to meet the following criteria: age ≥20 years; if symptomatic, LV ejection fraction (LVEF) ≥50% with or without the administration of cardioprotective drugs such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB)s, β-blockers, or mineralocorticoid receptor antagonists (MRA); if asymptomatic, LVEF ≥50% with at least

Table 1. Patient Characteristics at Baseline (n=16)	
Clinical characteristics	
Age (years)	64±14
Female sex	7 (44)
Body weight (kg)	63±14
SBP (mmHg)	136±22
DBP (mmHg)	77±18
Heart rate (beats/min)	85±11
Heart failure stage	
A	6 (37)
B	7 (44)
C	3 (19)
D	0 (0)
Blood examinations	
Hemoglobin (g/dL)	13.0±2.1
BUN (mg/dL)	16.3±6.2
Creatinine (mg/mL)	0.82±0.25
eGFR (mL/min/1.73 m²)	69.8±17.0
BNP (pg/mL)	30.1 [9.2–85.0]
AST (U/L)	23±7
ALT (U/L)	21±10
Total protein (g/dL)	7.1±0.6
Albumin (g/dL)	4.0 [3.7–4.2]
LDL-C (mg/dL)	115±37
HDL-C (mg/dL)	59±12
Triglyceride (mg/dL)	132 [91–167]
CRP (mg/dL)	0.1 [0.1–0.3]
Na (mmol/L)	141±2
K (mmol/L)	4.0±0.3
Comorbidities	
Hypertension	9 (56)
Diabetes	4 (25)
Dyslipidemia	7 (44)
Obesity	8 (50)
Smoking	1 (6)
Ischemic heart disease	3 (19)
History of admission for heart failure	2 (13)
Medications	
ACE inhibitors/ARBs	10 (63)
β-blockers	8 (50)
MRAs	1 (6)
Diuretics	3 (19)
CCBs	3 (19)
HFA-PEFF diagnostic algorithm	
≥5 points	3 (19)
2–4 points	9 (56)
≤1 point	4 (25)

Continuous variables are presented as the mean±SD for normally distributed data and as the median [interquartile range] for data that is not normally distributed. Categorical data are presented as n (%). ACE, angiotensin-converting enzyme; ALT, alanine aminotransferase; ARBs, angiotensin II receptor blockers; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MRAs, mineralocorticoid receptor antagonists; SBP, systolic blood pressure.

one risk factor for Stage A HF; resting HR ≥75 beats/min and potentially requiring additional administration of ivabradine; sinus rhythm; stable New York Heart Association (NYHA) functional classification and the administration of cardioprotective drugs (e.g., ACE inhibitors, ARBs, β-blockers, or MRAs) over the 4 weeks prior to study enrollment; and providing written informed consent to take part in the study.

After patients had provided informed consent, they were given 5 mg/day ivabradine for the duration of the study. Other drugs were not changed after ivabradine was started. Physical examinations were performed at baseline and 1, 2, and 3 months after starting ivabradine; 12-lead electrography, blood tests and echocardiography were performed at baseline and 3 months after starting ivabradine.

This trial was registered with the Japan Registry of Clinical Trials (jRCT; Registration no. jRCTs051200059), and posted information will be updated as needed to reflect protocol amendments and study progress. The study protocol was approved by the Ethics Committee of Kobe University Hospital Clinical and Translational Research Center (Reference no. C200006) and the study was conducted in accordance with the Declaration of Helsinki.

Echocardiographic Examinations

All patients underwent a resting standard echocardiographic examination using commercially available echocardiography systems. Standard echocardiographic measurements were obtained in accordance with the current guidelines of the American Society of Echocardiography/European Association of Cardiovascular Imaging.[6]

Two-Dimensional Speckle-Tracking Strain Analysis

Two-dimensional speckle-tracking strain analysis was performed for each patient using dedicated software (AutoSTRAIN, TOMTEC-ARENA; TOMTEC Imaging Systems, Munich, Germany) to evaluate LV longitudinal function, which was assessed in terms of global longitudinal strain (GLS). Briefly, apical 4-, 2- and long-axis views, obtained as Digital Imaging and Communications in Medicine (DICOM)-formatted file images, were uploaded onto a personal computer for subsequent off-line GLS analysis. GLS was determined as the averaged peak longitudinal strain of 16 LV segments, and expressed as an absolute value in accordance with current guidelines.

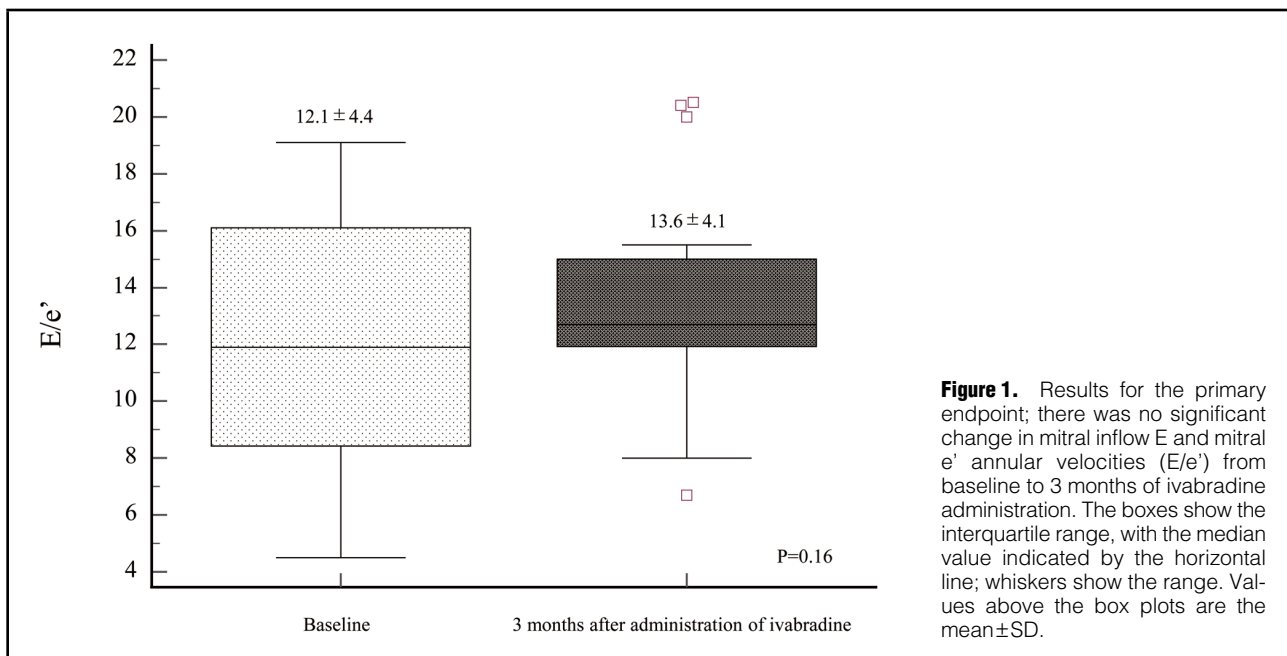### Primary and Secondary Endpoints

The primary endpoint was defined as a change in E/e' during ivabradine administration from baseline to 3 months. Secondary endpoints were changes in B-type natriuretic peptide (BNP), left atrial volume index (LAVI), or GLS over the same period.

Statistical Analysis

Continuous variables are expressed as the mean±SD for normally distributed data and as the median with interquartile range (IQR) for data that were not normally distributed. Categorical variables are expressed as frequencies and percentages. Parameters of the 2 groups during ivabradine administration from baseline to 3 months were compared using paired t-tests or the Wilcoxon signed-rank test, depending on data distribution. Proportional differences were evaluated using Fisher's exact test. Univariate linear correlation analysis was used to evaluate associa-

Table 2. Echocardiographic Parameters at Baseline and After 3 Months Administration of Ivabradine

Variable	Baseline	3 months after administration of ivabradine	P value
LVEDV (mL)	81.2±33.3	90.5±28.0	0.12
LVESV (mL)	26.9 [22.0–35.9]	32.9±13.1	0.17
LVEF (%)	64.2±7.7	64.2±6.8	0.66
LAVI (mL/m²)	38.7±17.5	44±17.1	0.34
IVST (mm)	8.6±2.0	8.9±1.6	0.66
PWT (mm)	9.3±1.8	9.6±1.7	0.58
LV volume index (g/m²)	81.6±31.4	81.6±25.7	0.54
E/e'	12.1±4.4	13.6±4.1	0.16
GLS (%)	17.1±3.5	18.6±3.6	0.01
Mitral regurgitation (≥moderate)	0 (0)	0 (0)	–
Atrial regurgitation (≥moderate)	0 (0)	0 (0)	–
Atrial stenosis (≥moderate)	0 (0)	0 (0)	–
Tricuspid regurgitation (≥moderate)	1 (6)	1 (6)	–

Unless indicated otherwise, data are given as the mean±SD for normally distributed data, median [interquartile range] for non-normally distributed data, or n (%) for categorical variables. E, peak early diastolic mitral flow velocity; e', spectral pulsed-wave Doppler-derived early diastolic velocity from the septal mitral annulus; GLS, global longitudinal strain; IVST, interventricular septum thickness; LAVI, left atrial volume index; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; PWT, posterior wall thickness; VLESV, left ventricular end-systolic volume.

Figure 1. Results for the primary endpoint; there was no significant change in mitral inflow E and mitral e' annular velocities (E/e') from baseline to 3 months of ivabradine administration. The boxes show the interquartile range, with the median value indicated by the horizontal line; whiskers show the range. Values above the box plots are the mean±SD.

tions between HR and GLS at baseline, as well as between changes in HR and GLS after the administration of ivabradine. In all cases, 2-sided P<0.05 was considered statistically significant. All analyses were performed using commercially available software (MedCalc version 19.6; MedCalc Software, Mariakerke, Belgium).
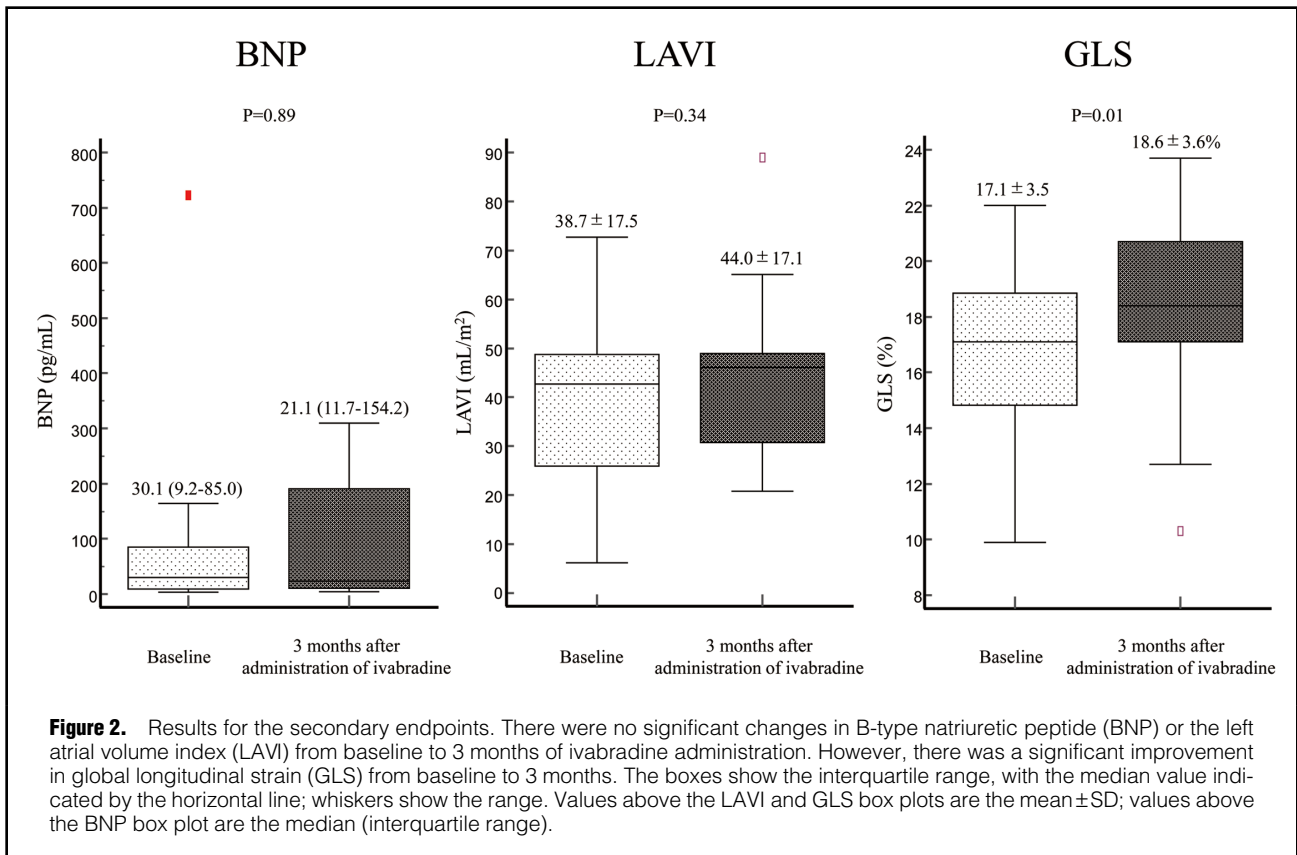
Results

Patient Characteristics
During the 18-month registration period, 16 patients were enrolled from 3 participating institutions (**Table 1**). After 3 months administration of 5 mg/day ivabradine, HR was significantly reduced from 85±11 to 76±13 beats/min (P=0.008). Three patients (19%) met the diagnostic criteria for HFpEF using the HFA-PEFF diagnostic algorithm (i.e., score ≥5 points).[7]

Changes in Symptoms After Administration of Ivabradine
All 4 patients with palpitation at baseline improved after 3 months administration of ivabradine (**Table 2**). Of 6 patients with shortness of breath at baseline, 5 (83%) improved after 3 months administration of ivabradine. Of 3 patients with dyspnea on exertion at baseline, 2 (67%) improved

Figure 2.   Results for the secondary endpoints. There were no significant changes in B-type natriuretic peptide (BNP) or the left atrial volume index (LAVI) from baseline to 3 months of ivabradine administration. However, there was a significant improvement in global longitudinal strain (GLS) from baseline to 3 months. The boxes show the interquartile range, with the median value indicated by the horizontal line; whiskers show the range. Values above the LAVI and GLS box plots are the mean±SD; values above the BNP box plot are the median (interquartile range).

after 3 months administration of ivabradine.

Primary Endpoint
No significant change was observed in E/e' after 3 months administration of 5 mg/day ivabradine (from 12.1±4.4 at baseline to 13.6±4.1 at 3 months; P=0.16; **Figure 1**).

Secondary Endpoints
Results for the secondary endpoints are shown in **Figure 2**. Compared with baseline, there were no significant changes after 3 months administration of 5 mg/day ivabradine in BNP (from 30.1 [9.2–85.0] to 21.1 [11.7–154.2] pg/mL; P=0.89) or LAVI (from 38.7±17.5 to 44.0±17.1 mL/m²; P=0.34). However, GLS improved significantly from 17.1±3.5% at baseline to 18.6±3.6% after 3 months administration of 5 mg/day ivabradine (P=0.01).

Association of HR With GLS
There was no significant relationship between HR and GLS at baseline (r=0.23, P=0.39) or between the relative change in HR and GLS after the administration of ivabradine (r=0.40, P=0.14).

Discussion

In this study, specified as clinical research in the Japanese context, ivabradine did not improve LV diastolic function as assessed by E/e'. BNP and LAVI did not improve either, but GLS improved significantly after the administration of ivabradine.

Effect of Ivabradine on LV Diastolic Function in HFpEF Patients
HFpEF usually presents as LV diastolic dysfunction, identifiable as the earliest functional alteration in the course of HFpEF. High HR may have a detrimental effect in HFpEF patients with LV diastolic dysfunction because of limited LV filling. Thus, reducing HR may be an attractive therapeutic strategy for HFpEF; however, there are no established opinions regarding the association of HR with LV diastolic function or the impact of lowering HR on LV diastolic function in patients with HFpEF. Among patients with HFpEF, those with higher resting HR had lower LV filling pressures and higher resting HR was associated with myocardial Ca²⁺ retention,[8] and HR lowering increased LV filling pressure.[9] There are no reports of large randomized controlled trials evaluating the effects of HR lowering with β-blockers or ivabradine on LV diastolic function in HFpEF patients. A recent randomized double-blind placebo-controlled trial including 179 symptomatic HFpEF patients with resting HR ≥70 beats/min in sinus rhythm found no significant change in E/e', regardless of a reduction in HR of 13.0 beats/min following ivabradine administration.[10] In the present IVA-PEF study, there was no significant change in E/e' after 3 months administration of 5 mg/day of ivabradine. Although HR was significantly reduced from 85±11 to 76±13 beats/min after 3 months administration of ivabradine, the reduction in HR was considered to be inadequate in the present study. This relatively high HR was probably due to the dose of ivabradine remaining unchanged at 5 mg/day throughout the study. In the J-SHIFT study, 70.9% patients in the ivabradine group

were on the highest dose of 15 mg/day, but even patients in that study did not reach the optimal target HR.[4]

Potential of Ivabradine for HFpEF Patients With High HR

HFpEF is associated with significant morbidity and mortality, and the findings of clinical trials have generally been disappointing, with no beneficial effects of medical treatment on mortality and marginal benefits on HF hospitalizations. Recent guidelines from the American College of Cardiology/American Heart Association provide new recommendations for pharmacological treatment of HFpEF with sodium-glucose cotransporter-2 inhibitors (Class IIa recommendation), MRAs (Class IIb recommendation), and angiotensin receptor-neprilysin inhibitors (Class IIb recommendation),[11] but the use of β-blockers is not recommended for the pharmacological treatment of HFpEF. Moreover, the utility of HR lowering, including the use of β-blockers, in improving the exercise capacity of patients with HFpEF remains questionable. Palau et al reported that β-blocker withdrawal improved maximum functional capacity in patients with HFpEF.[12] Kagami et al showed that shortening of the LV diastolic filling interval with increased HR during exercise did not limit cardiac output reserve or exercise capacity in patients with HFpEF, and concluded that the use of β-blockers may need to be reconsidered for patients with HFpEF.[13]

Because Stage A HF represents a high risk for progression to HFpEF, the implementation of HF prevention strategies is potentially useful for patients with Stage A HF. Furthermore, LV longitudinal myocardial dysfunction marked by low GLS has been identified even in Stage A HF patients, so that it should be currently considered the first marker of subclinical LV dysfunction, possibly leading to HFpEF. The present study did not show improvement in LV diastolic function after the administration of ivabradine because of several limitations discussed below, but GLS did improve significantly, so that a higher dose of ivabradine may have potential as a treatment for patients with Stage A HF with a resting HR ≥75 beats/min. An association of GLS with HR has been reported previously in patients with HFpEF. Peverill et al reported that GLS in patients with preserved LVEF and LV diastolic dysfunction was independently and inversely related to HR,[14] and worse GLS was significantly associated with higher HR in patients with HFpEF.[15] However, no explanation for these observations has been proposed. We previously reported a significant relationship between HR and GLS in patients with Stage A HF.[16] However, no significant relationships were observed between HR and GLS in the present study, probably due to the small number of patients.

Study Limitations

This study has several limitations. First, this study comprised a very small number of patients with a short follow-up period, so that future studies with larger patient populations and longer follow-up periods are needed to validate our findings. Second, the HR reduction was not satisfactory because the dose of ivabradine remained unchanged at 5 mg/day. Thus, future studies need to determine the optimal target HR without keeping the dose of ivabradine unchanged. Third, the HFpEF patients in this study included those with Stage A HF without overt HF, and only 19% of patients met the diagnostic criteria for HFpEF based on the HFA-PEFF diagnostic algorithm. However,

an increase in HR is also an independent risk factor for cardiovascular mortality and morbidity even in patients with Stage A HF.[1,2] Finally, baseline E/e' and BNP concentrations were low (12.1±4.4 and 30.1 [9.2–85.0] pg/mL, respectively) in this study, making it difficult to determine the effects of ivabradine.

Conclusions

In this study, ivabradine did not improve LV diastolic function in HFpEF patients with resting HR ≥75 beats/min in sinus rhythm, including those with Stage A HF. Thus, a further study is planned to address the limitations of this study.

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