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

Hidekazu Tanaka, MD, PhD; Yuki Yamauchi, MD; Junichi Imanishi, MD, PhD; Yutaka Hatani, MD, PhD; Susumu Odajima, MD; Hiroshi Okamoto, MD, PhD; Takatoshi Hayashi, MD, PhD; Ken-ichi Hirata, MD, PhD

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
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.

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)   |

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.

After patients had provided informed consent, they were given 5mg/day ivabradine for the duration of the study. Other drugs were not changed after ivabradine was started.

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-
Effect of Ivabradine on LV Diastolic Function

501

### Results

**Patient Characteristics**

During the 18-month registration period, 16 patients were enrolled from 3 participating institutions (Table 1). After 3 months administration of 5mg/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 HFP EF 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.
Effect of Ivabradine on LV Diastolic Function in HFrEF Patients

HFrEF usually presents as LV diastolic dysfunction, identifiable as the earliest functional alteration in the course of HFrEF. High HR may have a detrimental effect in HFrEF patients with LV diastolic dysfunction because of limited LV filling. Thus, reducing HR may be an attractive therapeutic strategy for HFrEF; 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 HFrEF. Among patients with HFrEF, those with higher resting HR had lower LV filling pressures and higher resting HR was associated with myocardial Ca²⁺ retention, and HR lowering increased LV filling pressure. 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 HFrEF patients. A recent randomized double-blind placebo-controlled trial including 179 symptomatic HFrEF 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. 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 HFP EF Patients With High HR**

HFP EF 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 HFP EF 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 \(\beta\)-blockers is not recommended for the pharmacological treatment of HFP EF. Moreover, the utility of HR lowering, including the use of \(\beta\)-blockers, in improving the exercise capacity of patients with HFP EF remains questionable. Palau et al reported that \(\beta\)-blocker withdrawal improved maximum functional capacity in patients with HFP EF.\(^12\) 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 HFP EF, and concluded that the use of \(\beta\)-blockers may need to be reconsidered for patients with HFP EF.\(^13\)

Because Stage A HF represents a high risk for progression to HFP EF, 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 HFP EF. 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 \(\geq 75\) beats/min. An association of GLS with HR has been reported previously in patients with HFP EF. 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 HFP EF.\(^15\) 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 HFP EF patients in this study included those with Stage A HF without overt HF, and only 19% of patients met the diagnostic criteria for HFP EF 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.\(^13\) 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 HFP EF patients with resting HR \(\geq 75\) beats/min in sinus rhythm, including those with Stage A HF. Thus, a further study is planned to address the limitations of this study.

**Sources of Funding**

This study did not receive any specific funding.

**Disclosures**

H.T. is a consultant for AstraZeneca plc, Ono Pharmaceutical Co., Ltd., Pfizer Inc, Otsuka Pharmaceutical Co., Ltd., and Novartis International AG. K.H. has received research funding from Daiichi Sankyo Co., Ltd., Actelion Pharmaceuticals Japan, Terumo Corporation, Abbott Vascular Japan, Otsuka Pharmaceutical Co., Ltd., Kowa Co., Ltd., Takeda Pharmaceutical Co., Ltd., Nihon Medi-Physics Co., Ltd., Novartis Pharma Co., Ltd., Bayer Co., Ltd., Biotronic Japan Co., Ltd., Fujifilm Toyama Chemical Co., Ltd., Medtronic Japan Co., Ltd., and Sysmex Co., Ltd. The remaining authors have no conflicts of interest to declare.

**IRB Information**

This study was approved by the Ethics Committee of Kobe University Hospital Clinical and Translational Research Center (Reference no. C200006).

**References**

1. Carnethon MR, Yan L, Greenland P, Garside DB, Dyer AR, Metzger B, et al. Resting heart rate in middle age and diabetes development in older age. *Diabetes Care* 2008; 31: 335 – 339.
2. Shigetoh Y, Adachi H, Yamagishi S, Enomoto M, Fukami A, Otsuka M, et al. Higher heart rate may predispose to obesity and diabetes mellitus: 20-year prospective study in a general population. *Am J Hypertens* 2009; 22: 151 – 155.
3. Bohm M, Swedberg K, Komajda M, Borner JS, Ford I, Dubost-Brama A, et al. Heart rate as a risk factor in chronic heart failure (SHIFT): The association between heart rate and outcomes in a randomised placebo-controlled trial. *Lancet* 2010; 376: 886 – 894.
4. Tsutsui H, Momomura SI, Yamashina A, Shimokawa H, Kihara Y, Saito Y, et al. Efficacy and safety of ivabradine in Japanese patients with chronic heart failure: J-SHIFT Study. *Circ J* 2019; 83: 2049 – 2060.
5. Tanaka H, Yamauchi Y, Imanishi J, Hatani Y, Hayashi T, Hirata K. Effect of ivabradine on left ventricular diastolic function of patients with heart failure with preserved ejection fraction: IVA-PEF study. *J Cardiol* 2021; 77: 641 – 644.
6. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015; 16: 233 – 270.
7. Pieske B, Tschope C, de Boer RA, Fraser AG, Anker SD, Donal E, et al. How to diagnose heart failure with preserved ejection fraction: The HFA-PEFF diagnostic algorithm: A consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J* 2020; 41: 3297 – 3317.
8. Silverman DN, Ramboz M, Lustgarten DL, Lobel R, LeWinter MM, Meyer M. Heart rate-induced myocardial Ca\(^{2+}\) retention and left ventricular volume loss in patients with heart failure with preserved ejection fraction. *J Am Heart Assoc* 2020; 9: e017215.
preserved ejection fraction: Time to slow beta-blocker use? Circ Heart Fail 2019; 12: e006213.

10. Komajda M, Isnard R, Cohen-Solal A, Metra M, Pieske B, Ponikowski P, et al. Effect of ivabradine in patients with heart failure with preserved ejection fraction: The EDIFY randomized placebo-controlled trial. Eur J Heart Fail 2017; 19: 1495–1503.

11. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: Executive Summary: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 2022; 79: 1757–1780.

12. Palau P, Seller J, Dominguez E, Sastre C, Ramon JM, de La Espriella R, et al. Effect of beta-blocker withdrawal on functional capacity in heart failure and preserved ejection fraction. J Am Coll Cardiol 2021; 78: 2042–2056.

13. Kagami K, Obokata M, Harada T, Kato T, Wada N, Adachi T, et al. Diastolic filling time, chronotropic response, and exercise capacity in heart failure and preserved ejection fraction with sinus rhythm. J Am Heart Assoc 2022; 11: e026009.

14. Peverill RE, Cheng K, Cameron J, Donelan L, Mottram PM. Relationships of global longitudinal strain with s', long-axis systolic excursion, left ventricular length and heart rate. PLoS One 2020; 15: e0235791.

15. Kraigher-Krainer E, Shah AM, Gupta DK, Santos A, Claggett B, Pieske B, et al. Impaired systolic function by strain imaging in heart failure with preserved ejection fraction. J Am Coll Cardiol 2014; 63: 447–456.

16. Yamauchi Y, Tanaka H, Yokota S, Mochizuki Y, Yoshigai Y, Shiraki H, et al. Effect of heart rate on left ventricular longitudinal myocardial function in type 2 diabetes mellitus. Cardiovasc Diabetol 2021; 20: 87.