Vascular Endothelial Growth Factor Inhibitors Impair Left Ventricular Diastolic Functions

Haruka Yokoyama, Wataru Shioyama, MD, Takuya Shintani, PhD, Shinichiro Maeda, Sachiko Hirobe, PhD, Makiko Maeda, PhD, Yasushi Sakata, MD and Yasushi Fujio, MD

Summary

Vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) frequently induce cardiovascular adverse events, though VEGFR-TKIs contribute to the improvement of the prognosis of patients with malignancies. It is widely accepted that VEGFR-TKIs impair left ventricular systolic functions; however, their effects on diastolic functions remain to be fully elucidated. The purpose of this study was to analyze the impact of VEGFR-TKIs on left ventricular diastolic functions. This study was designed as a retrospective single-center cohort study in Japan. We assessed 24 cases who received VEGFR-TKI monotherapy (sunitinib, sorafenib, pazopanib, axitinib) with left ventricular ejection fraction (LVEF) above 50% during the therapy at the Osaka University Hospital from January 2008 to June 2019. Left ventricular diastolic functions were evaluated by the change in echocardiographic parameters before and after the VEGFR-TKI treatment. Both septal e’ and lateral e’s decreased after treatment (septal e’: before, 6.1 ± 1.8; after, 5.0 ± 1.9; n = 21, P < 0.01; lateral e’: before, 8.7 ± 2.8; after, 6.9 ± 2.3; n = 21, P < 0.01). E/A declined after VEGFR-TKIs administration, though not statistically significantly. In 20 cases with at least one risk factor for heart failure with preserved ejection fraction (HFpEF), E/A significantly decreased (0.87 ± 0.34 versus 0.68 ± 0.14; P < 0.05) as well as the septal and lateral e’s. These results suggest that treatment with VEGFR-TKIs impairs left ventricular diastolic functions in patients with preserved LVEF, especially in those with risk factors for HFpEF.

Key words: Cardio-oncology, Diastolic dysfunction, HFpEF, VEGFR-TKIs, Sunitinib

During the last 20 years, various classes of tyrosine kinase inhibitors (TKIs) have been developed and contributed to the improvement of the clinical outcomes of patients with malignancies.1,2 Vascular endothelial growth factor receptor tyrosine (VEGFR)-TKIs, which suppress tumor angiogenesis, show beneficial effects in the treatment of a wide range of solid malignancies, and the indications for their use have been increasing.2,3 However, VEGFR-TKIs show serious adverse events in cardiovascular systems, including hypertension, thrombosis, and left ventricular systolic dysfunction (LVSD).4,5 Among cardiovascular adverse events, much attention has been paid to LVSD because VEGFR-TKIs-induced LVSD often results in severe heart failure,5 which limits the continuation of VEGFR-TKI therapy.

Because of the structural similarities between receptor tyrosine kinases, some VEGFR-TKIs exhibit inhibitory effects on multiple receptor tyrosine kinases in addition to VEGF-tyrosine kinase.2 For example, sunitinib, a widely-used oral VEGFR-TKI, inhibits all 3 VEGFRs, platelet-derived growth factor receptors α and β, stem cell factor receptor cKIT, colony-stimulating factor 1 receptor, fms-like tyrosine kinase receptor 3, and ret oncogene product, though the anti-tumor effects of VEGFR-TKIs are largely explained by the inhibition of VEGFR-2. In tumor angiogenesis, VEGF is produced by tumor cells that are exposed to hypoxic conditions. VEGF activates the phosphoinositide 3-kinase and its downstream serine protein kinase (Akt) through VEGFR-2 in endothelial cells and stimulates endothelial nitric oxide synthase activity, leading to upregulation of NO production.6,7 Since NO production is essential for VEGF-mediated angiogenesis and for maintenance of vascular homeostasis, the inhibition of the VEGF signaling pathway impairs neovascularization and reduces blood supply to tumor cells, resulting in the suppression of tumor growth.

Left ventricular diastolic dysfunction (LVDD) is another leading cause of heart failure. Indeed, heart failure...
**Table 1. Inclusion and Exclusion Criteria**

| Criteria     | Inclusion criteria                                                                 |
|--------------|-----------------------------------------------------------------------------------|
|              | 1. VEGFR-TKI monotherapy was given.                                                |
|              | 2. Echocardiographic examination was performed both before and after VEGFR-TKI treatment. |
|              | 3. LVEF was greater than 50% during the therapy.                                   |
| Exclusion criteria | 1. Atrial fibrillation.                                                            |
|              | 2. Invasion of the cardiac tissue by the tumor.                                    |
|              | 3. Medication was changed to other classes of anti-cancer drugs during the interval between echocardiographic studies. |

VEGFR-TKI indicates vascular endothelial growth factor receptor-tyrosine kinase inhibitor; and LVEF, left ventricular ejection fraction.

**Figure 1.** Study cohort. Study subjects were selected from 218 patients treated with vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs), such as sunitinib, sorafenib, pazopanib, axitinib, regorafenib, and lenvatinib, according to inclusion and exclusion criteria. LVEF indicates left ventricular ejection fraction; and AF, atrial fibrillation.

with preserved ejection fraction (HFrEF) accounts for 40% of the cases of heart failure. The molecular mechanisms of HFrEF remain to be fully elucidated, probably because HFrEF is likely to be caused by multiple factors. Interestingly, diabetic cardiomyopathic hearts showed the reduced expression of VEGF with LVDD and the replenishment of VEGF expression ameliorated cardiac function. These data indicate that VEGF-mediated signaling plays important roles in the onset of LVDD associated with diabetic cardiomyopathy, suggesting that blockade of the VEGF signaling pathway by VEGFR-TKIs influences diastolic function in the clinical setting.

In this study, to address the relationship between VEGF signaling and left ventricular diastolic function, we examined the effects of the blockade of VEGF signaling on left ventricular diastolic function in patients treated with VEGFR-TKIs. We found that VEGFR-TKIs treatment impaired left ventricular diastolic functions, especially in patients with risk factors for HFrEF.

**Methods**

This study was designed as a retrospective, single-center, observational study conducted at the Osaka University Hospital, Osaka, Japan. The study was approved by the Ethical Review Committee of Osaka University (approval number, 19271) and by that of the Graduate School of Pharmaceutical Sciences, Osaka University (approval number, yakuhiito2019-20).

**Study population:** The electronic medical records of 218 patients who had been treated with VEGFR-TKIs (sunitinib, sorafenib, pazopanib, axitinib, regorafenib, and lenvatinib) at the Osaka University Hospital from January 2008 to June 2019 were reviewed. The inclusion and exclusion criteria are shown in Table I. Patients with atrial fibrillation were excluded because E/A cannot be evaluated for lack of atrial systolic phase. The flowchart for patient recruitment is shown in Figure 1. Among 218 patients, 40 underwent echocardiography both before and after VEGFR-TKI treatment. Ejection fraction was pre-
served (LVEF > 50%) in 35 patients. Six subjects were excluded due to atrial fibrillation and/or invasion of the cardiac tissue by the tumor. In 5 patients, VEGFR-TKI monotherapy was changed to therapy with other classes of anti-cancer drugs during the interval between echocardiographic studies. Thus, the clinical data of 24 patients were analyzed in this study.

As per previous studies,10-12 we considered age > 65 years old, body mass index ≥ 25 kg/m², smoking, diabetes mellitus, and history of myocardial infarction as risk factors for HFpEF.

**Echocardiography:** Echocardiographic data were extracted from the medical records within 1 year before VEGFR-TKI therapy initiation and within 50 days after the nearest administration. Echocardiographic parameters were compared between before and after VEGFR-TKI treatment according to the Guidelines for Diagnosis and Treatment of Acute and Chronic Heart Failure (JCS 2017/ JHFS 2017). LVEF was obtained using the Simpson’s method.

**Statistical analysis:** Statistical analyses were performed using JMP pro 15.0 (SAS Institute, Cary, NC, USA). Differences within and between groups were calculated using the Student’s t-, paired t-, or Pearson’s chi-square test. Nonparametric comparisons were performed using the Wilcoxon signed-rank or Wilcoxon rank sum test. Correlations between variables were tested with Pearson’s correlation coefficient. Nonparametric comparisons were performed using Spearman’s rank correlation coefficient. Results were expressed as median (range) or mean ± standard deviation, and P < 0.05 was considered statistically significant.

**Results**

The clinical profile of the total number of patients treated with VEGFR-TKIs (n = 218) and of the study subjects (n = 24) is shown in Table II. There was no significant difference between the total number of patients and the study subjects in terms of background, indicating that the selection of the study subjects was not biased. About half of the patients were treated with sunitinib (all patients, 50.0%; study subjects, 54.2%). Renal cell carcinoma accounted for half of the cases (all patients, 48.2%; study subjects, 54.2%). In the study subjects, anti-hypertensive drugs were given to 58.3% of the patients at the start of VEGFR-TKI treatment and to 91.7% at the end of the observation period as concomitant medications. The duration of VEGFR-TKI monotherapy between echocardiographic examinations was 234 ± 264 (range: 13-1122) days.

During the observation period, the general condition of patients approached cancer cachexia, diagnosed from the reduction of serum albumin, increased CRP, and decreased hemoglobin (Table III). The mean blood pressure was not significantly increased, probably because anti-hypertensive drugs were appropriately given, as described above. The incidence of arrhythmia was not described in the medical record.

Echocardiographic analysis demonstrated that VEGFR-TKIs tended to decrease LVEF, which was however, not significant in the total study population (before, 69.1 ± 7.7; after, 65.8 ± 6.2; n = 24, P = 0.06; Table III). Among the 4 kinds of VEGFR-TKIs used in this study population, sunitinib significantly reduced LVEF (sunitinib: before, 71.8 ± 7.9; after, 65.2 ± 5.4; n = 13, P < 0.05; others: before, 65.9 ± 6.3; after 66.5 ± 7.1; n = 11, P = 0.72; Table IV). Consistently, the change in LVEF was larger in patients treated with sunitinib than in those with other VEGFR-TKIs (sunitinib versus others, −6.6 ± 9.4 versus +0.6 ± 4.5; P = 0.039; Table V). Since this study was designed to address the effects of VEGFR-TKIs on diastolic function, we selected patients with LVEF above 50% during the administration period. Therefore, the reduction of LVEF was subclinical. Indeed, no study subject showed symptomatic heart failure during the administration period according to the medical records.

One of the most important findings of this study is that both the septal and lateral e’s significantly decreased during VEGFR-TKI treatment (septal e’: before, 6.1 ± 1.8; after, 5.0 ± 1.9; n = 21, P < 0.01; lateral e’: before, 8.7 ± 2.8; after, 6.9 ± 2.3; n = 21, P < 0.01; Table III, Figure 2). In a subanalysis, the decrease in the septal and lateral e’s was also observed even if the study population included patients with atrial fibrillation that were excluded from the main analysis (Supplemental Table). Since hypertension and anemia are risk factors of diastolic dysfunction, we examined the association between diastolic dysfunction and changes in blood pressure (Figure 3) or hemoglobin (Figure 4) and found that neither of these parameters was associated with diastolic dysfunction. In contrast to LVEF, there was no significant difference in the changes in the septal and lateral e’s between sunitinib and others (sunitinib versus others, ΔSeptal e’: −1.0 ± 1.4 versus −1.1 ± 1.1, P = 0.696; ΔLateral e’: −2.1 ± 1.8 versus −1.6 ± 2.4, P = 0.619; Table V).

Finally, we selected patients with more than one risk factor for HFpEF, as described in the Methods section, and evaluated the diastolic functions (Table VI). As is the case of the total population, both septal and lateral e’s significantly decreased (septal e’: before, 5.7 ± 1.7; after, 4.7 ± 1.6, n = 17, P < 0.01; lateral e’: before, 8.3 ± 2.3; after, 6.5 ± 1.5; n = 17, P < 0.01). Moreover, the decrease in E/A was also observed during treatment (before, 0.87 ± 0.34; after, 0.68 ± 0.14; n = 18, P < 0.05).

**Discussion**

In this study, we analyzed the impact of VEGFR-TKIs on left ventricular diastolic function by assessing patients with preserved LVEF who were treated with VEGFR-TKI monotherapy. The parameters of diastolic function, septal and lateral e’s values, significantly decreased after treatment. E/A was also reduced in patients with risk factor(s) for HFpEF. These results indicate that VEGFR-TKIs impair left ventricular diastolic functions, especially in patients with risk factors for HFpEF.

Recently, Catino et al. clearly demonstrated that sunitinib results in the impairment of vascular functions with the increase in blood pressure, and those baseline vascular functions (total peripheral resistance, arterial elastance and aortic impedance) were associated with dia-
Table II. Background of the Patients

|                                | Patients treated with VEGFR-TKI (n = 218) | Study subjects (n = 24) | P value |
|--------------------------------|-----------------------------------------|------------------------|---------|
| Age, years                     | 66 (20–86)                              | 68 (44–79)             | 0.307   |
| ≥ 65                           | 123 (56.4%)                             | 14 (58.3%)             | 0.858   |
| Males                          | 152 (69.7%)                             | 19 (79.2%)             | 0.335   |
| BMI, kg/m²                     | 22.2 (16.3–36.7)                        | 23.1 (17.7–28.7)       | 0.400   |
| ≥ 25                           | 44 (20.2%)                              | 8 (33.3%)              | 0.137   |
| N/R                            | 1 (0.5%)                                | 0                      |         |
| Smoking                        | 29 (13.3%)                              | 3 (12.5%)              | 0.756   |
| N/R                            | 31 (14.2%)                              | 1 (4.2%)               |         |
| Primary disease                |                                          |                        |         |
| Renal cell carcinoma           | 105 (48.2%)                             | 13 (54.2%)             | 0.577   |
| Hepatocellular carcinoma       | 40 (18.3%)                              | 6 (25.0%)              | 0.431   |
| Malignant soft tissue tumor    | 28 (12.8%)                              | 2 (8.3%)               | 0.525   |
| GIST                           | 23 (10.6%)                              | 2 (8.3%)               | 0.735   |
| Colorectal cancer              | 9 (4.1%)                                | 0                      | 0.310   |
| Pancreatic neuroendocrine      | 6 (2.8%)                                | 1 (4.2%)               | 0.695   |
| Thyroid carcinoma              | 5 (2.3%)                                | 0                      | 0.453   |
| Thymic carcinoma               | 2 (1.0%)                                | 0                      | 0.638   |
| VEGFR-TKI                      |                                          |                        |         |
| Sunitinib                      | 109 (50.0%)                             | 13 (54.2%)             | 0.698   |
| Sorafenib                      | 50 (22.9%)                              | 7 (29.2%)              | 0.495   |
| Pazopanib                      | 28 (12.8%)                              | 2 (8.3%)               | 0.525   |
| Axitinib                       | 14 (6.4%)                               | 2 (8.3%)               | 0.721   |
| Others                         | 17 (7.8%)                               | 0                      | 0.156   |
| Medical history/complications during VEGFR-TKI treatment |                                  |                        |         |
| Hypertension                   | 107 (49.1%)                             | 14 (58.3%)             | 0.390   |
| Diabetes                       | 84 (38.5%)                              | 7 (29.2%)              | 0.369   |
| IHDs                           |                                       |                        |         |
| Myocardial infarction          | 4 (1.8%)                                | 0 (0%)                 | 0.503   |
| Angina                         | 39 (17.9%)                              | 2 (8.3%)               | 0.236   |
| Medication for CVDs at the initiation of VEGFR-TKI treatment |                                  |                        |         |
| Ca-blocker                     | 70 (32.1%)                              | 9 (37.5%)              | 0.593   |
| ARB                            | 46 (21.1%)                              | 7 (29.2%)              | 0.365   |
| ACEI                           | 6 (2.8%)                                | 2 (8.3%)               | 0.147   |
| Diuretics                      | 29 (13.3%)                              | 2 (8.3%)               | 0.489   |
| β blockler                     | 19 (8.7%)                               | 1 (4.2%)               | 0.442   |
| α1 blockler                    | 2 (0.9%)                                | 0                      | 0.638   |
| Others                         | 9 (4.1%)                                | 0                      | 0.310   |
| No medication                  | 105 (48.2%)                             | 10 (41.7%)             | 0.545   |

Values are median (range) or n (%). VEGFR-TKI indicates vascular endothelial growth factor receptor-tyrosine kinase inhibitor; N/R, no records; BMI, body mass index; GIST, gastrointestinal stromal tumor; IHD, ischemic heart disease; CVD, cardiovascular disease; ARB, angiotensin receptor blocker; and ACEI, angiotensin-converting enzyme inhibitor.

Further large-scale studies would be required to clarify the differences observed in the effects of VEGFR-TKIs on cardiac functions.

Left ventricular diastolic function is influenced by multiple factors. Interestingly, recent studies have demonstrated that microvascular dysfunction is closely associated with HFpEF; however, their causal relationship remains to be fully demonstrated. VEGF contributes not only to the promotion of angiogenesis but also to the maintenance of vascular homeostasis by NO production. Thus, VEGFR-TKIs are likely to induce diastolic dysfunction by disturbing vascular function, as is the case with hypertension, one of the most common adverse events in patients treated with VEGFR-TKIs. Our findings might provide insights into the causality between ventricular diastolic dysfunction and vascular dysfunction.
be required to address whether diastolic dysfunction could sunitinib acutely induces diastolic dysfunction, but does uutes to predict systolic dysfunction. In an animal model, clear whether the evaluation of diastolic function contrib-
on diastolic function. It would be informative to make on diastolic dysfunction were excluded in order to focus on diastolic function precedes systolic dysfunction in dia-
getic cardiomyopathy.9) Further prospective studies would  

| Table III. Comparison of Echocardiographic Parameters and General Condition Between Before and After VEGFR-TKI Treatment in Study Subjects (n = 24) |
|---|
| **Echocardiography** |
| **Parameter** | **Before** | **After** | **P value** |
| LVEF, % | 24 | 69.1 ± 7.7 | 65.8 ± 6.2 | 0.060 |
| LAD, mm | 23 | 35.1 ± 6.9 | 35.8 ± 7.0 | 0.310 |
| LVDd, mm | 24 | 46.3 ± 4.7 | 46.0 ± 4.9 | 0.809 |
| LVDs, mm | 23 | 27.9 ± 3.5 | 28.9 ± 3.4 | 0.276 |
| E/A | 23 | 0.86 ± 0.35 | 0.76 ± 0.31 | 0.214 |
| DT, m/second | 21 | 233 ± 64 | 235 ± 82 | 0.901 |
| Mean E/e’ | 21 | 9.2 ± 3.0 | 10.2 ± 3.4 | 0.144 |
| Septal e’, cm/second | 21 | 6.1 ± 1.8 | 5.0 ± 1.9 | 0.001 |
| Lateral e’, cm/second | 21 | 8.7 ± 2.8 | 6.9 ± 2.3 | < 0.001 |
| HR, bpm | 20 | 70.5 ± 10.1 | 71.8 ± 14.3 | 0.678 |
| **General Condition** |
| **Parameter** | **Before** | **After** | **P value** |
| BMI, kg/m² | 24 | 23.1 (17.7–28.7) | 22.2 (17.5–27.5) | 0.093 |
| Body temperature, °C | 21 | 36.4 (35.8–37.0) | 36.5 (35.5–37.1) | 0.286 |
| MBP, mmHg | 24 | 89.1 (63.3–114.3) | 96.7 (58.3–113.3) | 0.167 |
| Alb, g/dL | 24 | 3.9 ± 0.5 | 3.4 ± 0.7 | 0.001 |
| Hb, g/dL | 24 | 12.7 ± 2.2 | 11.8 ± 1.8 | 0.044 |
| Ccr, mL/minute | 24 | 61.8 ± 23.6 | 58.1 ± 28.1 | 0.435 |

Values are median (range) or mean ± standard deviation. VEGFR-TKI indicates vascular endothelial growth factor receptor-tyrosine kinase inhibitor; LVEF, left ventricular ejection fraction; LAD, left atrial dimension; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; E/A, peak velocity of E-wave/peak velocity of A-wave; DT, deceleration time; E/e’, peak velocity of E-wave/peak velocity of e’-wave; e’, peak velocity of e’-wave; HR, heart rate; BMI, body mass index; MBP, mean blood pressure; Alb, albumin; Hb, hemoglobin; and Ccr, creatinine clearance.

| Table IV. Comparison of Echocardiographic Parameters Between Before and After Sunitinib or Other VEGFR-TKI Treatment |
|---|
| **Parameter** | **Sunitinib** | **Others** |
| **n** | **Before** | **After** | **P value** | **n** | **Before** | **After** | **P value** |
| LVEF, % | 13 | 71.8 ± 7.9 | 65.2 ± 5.4 | 0.029 | 11 | 65.9 ± 6.3 | 66.5 ± 7.1 | 0.715 |
| LAD, mm | 13 | 34.0 ± 8.0 | 34.8 ± 8.0 | 0.336 | 10 | 36.5 ± 5.1 | 37.1 ± 5.5 | 0.680 |
| LVDd, mm | 13 | 45.6 ± 5.7 | 45.9 ± 5.5 | 0.747 | 11 | 47.0 ± 3.4 | 46.0 ± 4.4 | 0.781 |
| LVDs, mm | 13 | 26.6 ± 3.8 | 29.4 ± 3.4 | 0.045 | 10 | 29.6 ± 2.3 | 28.3 ± 3.4 | 0.266 |
| E/A | 13 | 0.81 ± 0.25 | 0.81 ± 0.38 | 1.00 | 10 | 0.92 ± 0.45 | 0.69 ± 0.16 | 0.160 |
| DT, m/second | 13 | 224 ± 68 | 240 ± 89 | 0.444 | 8 | 247 ± 58 | 226 ± 74 | 0.641 |
| Mean E/e’ | 12 | 8.4 ± 2.7 | 10.4 ± 3.8 | 0.081 | 9 | 10.3 ± 3.1 | 10.0 ± 3.1 | 0.496 |
| Septal e’, cm/second | 12 | 6.6 ± 1.8 | 5.5 ± 2.1 | 0.033 | 9 | 5.5 ± 1.7 | 4.3 ± 1.4 | 0.023 |
| Lateral e’, cm/second | 12 | 9.5 ± 2.7 | 7.4 ± 2.9 | 0.001 | 9 | 7.8 ± 2.7 | 6.2 ± 1.0 | 0.082 |
| HR, bpm | 10 | 78.1 ± 6.6 | 77.6 ± 14.7 | 0.586 | 10 | 62.9 ± 6.4 | 65.9 ± 11.9 | 0.625 |

Values are mean ± standard deviation. VEGFR-TKI indicates vascular endothelial growth factor receptor-tyrosine kinase inhibitor; LVEF, left ventricular ejection fraction; LAD, left atrial dimension; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; E/A, peak velocity of E-wave/peak velocity of A-wave; DT, deceleration time; E/e’, peak velocity of E-wave/peak velocity of e’-wave; e’, peak velocity of e’-wave; and HR, heart rate.

This study has a retrospective design and patients with systolic dysfunction were excluded in order to focus on diastolic function. It would be informative to make clear whether the evaluation of diastolic function contributes to predict systolic dysfunction. In an animal model, sunitinib acutely induces diastolic dysfunction, but does not alter systolic function.18) Interestingly, the impairment of diastolic function precedes systolic dysfunction in dia-
getic cardiomyopathy.9) Further prospective studies would be required to address whether diastolic dysfunction could be a predictor of heart failure in patients treated with VEGFR-TKIs.

The limitation of this study is that no patients with symptomatic HFpEF were observed in the study group. Consistently, the change in LAD was not detected during the observation period. Therefore, the impairment of dia-
istic function by VEGFR-TKIs was subclinical in this study, and its clinical significance is currently unknown. Nonetheless, our data suggest that the adverse effects of VEGFR-TKIs should be carefully evaluated in patients with a history of HFpEF. Another limitation of our study is that the diastolic function was analyzed for each single parameter. This study was conducted as a retrospective study using actual clinical data. As a result, there are too
### Table V. Comparison of the Changes in Echocardiographic Parameters Between Sunitinib and Other VEGFR-TKI Treatment

| Change                  | Sunitinib | Others | P value |
|-------------------------|-----------|--------|---------|
| ΔLVEF,%                 | −6.6 ± 9.4| + 0.6 ± 4.5| 0.039   |
| ΔLAD, mm                | + 0.8 ± 2.7| + 0.6 ± 3.9| 0.900   |
| ΔLVDD, mm               | + 0.3 ± 6.0| −1.0 ± 5.8| 0.771   |
| ΔLVDS, mm               | + 2.8 ± 4.0| −1.3 ± 3.6| 0.025   |
| ΔE/A                    | 0.00 ± 0.24| −0.24 ± 0.43| 0.107   |
| ΔDT, m/second           | + 17 ± 61| −21 ± 96| 0.232   |
| ΔMean E/e'              | + 1.9 ± 3.1| −0.3 ± 2.1| 0.081   |
| ΔSeptal e', cm/second   | −1.0 ± 1.4| −1.1 ± 1.1| 0.696   |
| ΔLateral e', cm/second  | −2.1 ± 1.8| −1.6 ± 2.4| 0.619   |
| ΔHR, bpm                | −0.5 ± 14.7| + 3.0 ± 11.9| 0.405   |

Values are mean ± standard deviation. VEGFR-TKI indicates vascular endothelial growth factor receptor-tyrosine kinase inhibitor; LVEF, left ventricular ejection fraction; LAD, left atrial dimension; LVDD, left ventricular end-diastolic diameter; LVDS, left ventricular end-systolic diameter; E/A, peak velocity of E-wave/peak velocity of A-wave; DT, deceleration time; E/e’, peak velocity of E-wave/peak velocity of e’-wave; e’, peak velocity of e’-wave; and HR, heart rate.

**Figure 2.** Changes in the septal and lateral e’s. The change in the septal (A) and lateral (B) e’s of each patient was shown. The mean e’s are indicated as the cross marks in the boxes. Both septal and lateral e’s significantly decreased during treatment (P < 0.01). Statistical analyses were performed using paired t-test.

**Figure 3.** The change in mean blood pressure (ΔMBP) was not correlated with that in the septal or lateral e’. The ΔMBP and septal (A, Δseptal e’) or lateral e’ (B, Δlateral e’) of each patient are shown. There was no correlation between ΔMBP and changes in the left ventricular diastolic functions (septal e’: P = 0.919; lateral e’: P = 0.905). Values of P were calculated using Pearson’s correlation coefficient.
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Table VI. Comparison of Echocardiographic Parameters Before and After VEGFR-TKI Treatment in Study Subjects with One or More Risk Factor (s) for HFpEF (n = 20)

| Parameter | Before | After | P value |
|-----------|--------|-------|---------|
| LVEF, %   | 69.3 ± 7.8 | 66.7 ± 5.7 | 0.389   |
| LAD, mm   | 36.7 ± 6.4 | 37.3 ± 6.5 | 0.432   |
| LVDD, mm  | 46.7 ± 4.7 | 45.6 ± 5.0 | 0.400   |
| LVDs, mm  | 28.1 ± 3.4 | 28.3 ± 2.8 | 0.827   |
| E/A       | 0.87 ± 0.34 | 0.68 ± 0.14 | 0.017   |
| DT, m/second | 236 ± 69 | 241 ± 83 | 0.807   |
| Mean E/e' | 10.1 ± 2.5 | 10.4 ± 3.5 | 0.619   |
| Septal e', cm/second | 5.7 ± 1.7 | 4.7 ± 1.6 | 0.005   |
| Lateral e', cm/second | 8.3 ± 2.3 | 6.5 ± 1.5 | < 0.001 |
| HR, bpm   | 70.0 ± 10.7 | 71.4 ± 14.6 | 0.681   |

Values are mean ± standard deviation. VEGFR-TKI indicates vascular endothelial growth factor receptor-tyrosine kinase inhibitor; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; LAD, left atrial dimension; LVDD, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; E/A, peak velocity of E-wave/peak velocity of A-wave; DT, deceleration time; E/e', peak velocity of E-wave/peak velocity of e'-wave; e', peak velocity of e'-wave; and HR, heart rate.

Figure 4. The change in hemoglobin (Hb) was not correlated with that in the septal or lateral e'. The change in hemoglobin (ΔHb) and septal e' (A, Δseptal e') or lateral e' (B, Δlateral e') of each patient was shown. Though Hb significantly decreased during treatment, there was no correlation between ΔHb and the changes in left ventricular diastolic parameters (septal e': P = 0.064; lateral e': P = 0.371). The P values were calculated using the Spearman’s rank correlation coefficient.

Disclosure

Conflicts of interest: All authors declare that they have no conflict of interest.

Contributions: Conceived and designed the study: HY, WS, YS, YF; Collected the data: HY, TS; Analyzed the data: HY, TS, SM, SH, MM; and Wrote the paper: HY, YF.

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Supplemental Files

Supplemental Table

Please see supplemental files; https://doi.org/10.1536/ihj.21-307