Riser Pattern Is a Novel Predictor of Adverse Events in Heart Failure Patients With Preserved Ejection Fraction

Takahiro Komori, MD; Kazuo Eguchi, MD, PhD; Toshinobu Saito, MD, PhD; Satoshi Hoshide, MD, PhD; Kazuomi Kario, MD, PhD

Background: The cardiovascular prognosis of heart failure with preserved ejection fraction (HFpEF) has been shown to be similar to that of heart failure with reduced ejection fraction (HFrEF). It is unknown which factors predict cardiovascular outcome in HFpEF. We tested the hypothesis that the abnormal pattern of circadian blood pressure (BP) rhythm known as the riser BP pattern is associated with adverse outcomes in HFpEF.

Methods and Results: We performed a prospective, observational cohort study of hospitalized HF patients who underwent ambulatory BP monitoring (ABPM). Five hundred and sixteen hospitalized HF patients (age, 69±13 years; male, n=321 [62%]; female, n=195 [38%]) were followed up for a median 20.9 months. The composite outcome consisting of all-cause mortality and cardiovascular events was observed in 220 patients. On Kaplan-Meier analysis, the riser BP pattern subgroup had a significantly higher incidence of the composite outcome than the other subgroups of HFpEF patients (HR, 3.01; 95% CI: 1.54–6.08, P<0.01), but not the HFrEF patients.

Conclusions: The riser BP pattern was found to be a novel predictor of cardiovascular outcome in HFpEF patients.

Key Words: Blood pressure measurement/monitoring; Circadian rhythm; Heart failure; Outcome

The prevalence of heart failure (HF) has increased to the point that HF is now a significant social burden in modern societies. Despite recent medical progress, the poor prognosis of HF is unchanged, and the prognosis worsens with advancing stage of HF. HF with preserved ejection fraction (HFpEF) is observed in approximately one-half of patients with HF, and its prognosis is as poor as that of HF with reduced ejection fraction (HFrEF). The management of HFpEF is one of the important unresolved issues in current cardiology practice.

The characteristics of patients with HFpEF and those with HFrEF are very different. HFpEF patients have been reported to be older, more frequently female, and with higher prevalences of hypertension, atrial fibrillation, and diabetes compared with HFrEF patients. Non-cardiac comorbidities such as chronic obstructive lung disease, anemia, chronic kidney disease, and malignancy are also frequently seen in HFpEF patients. HFpEF patients have significantly higher blood pressure (BP) and a significantly higher prevalence of abnormal circadian BP rhythm, such as riser BP pattern compared with HFrEF patients.

The factors associated with adverse outcome in HFpEF patients are not well established, but high N-terminal pro-B-type natriuretic peptide level, older age, the presence of diabetes, previous hospitalization for HF, chronic obstructive lung disease, and a low estimated glomerular filtration rate are associated with adverse outcome.

With regard to BP, it was reported that in HFpEF patients, low diastolic BP (DBP) was associated with adverse outcome, but systolic BP (SBP) was not. Abnormalities in an individual’s BP profile may be one of the major prognostic factors for HFpEF, but it is unclear which type of BP abnormality – that is, BP level, BP variability, and circadian BP rhythm – is associated with prognosis in HFpEF patients. Among such abnormalities, we focused on the riser pattern, a paradoxical increase in BP during sleep that exceeds that when awake.

The riser BP pattern was associated with adverse outcome in patients with diabetes and hypertension. Although a single report showed that the riser BP pattern was associated with adverse prognosis in HFrEF patients, the clinical significance of abnormal circadian BP rhythm has not been established in patients with HF. Thus, we tested the hypothesis that the riser BP pattern is associated with adverse outcome in HF patients, especially those with HFpEF, by conducting an analysis of the database of the updated hospital HF cohort at Jichi Medical University Hospital.
Methods

Study Design
We performed an observational, prospective cohort study of HF patients hospitalized from July 2007 to May 2014. The cohort was almost the same as that of our previous study. The study patients were diagnosed as having HF and were hospitalized in 1 of 5 institutions in Tochigi, Japan (Jichi Medical University Hospital; International University of Health and Welfare Hospital; International University of Health and Welfare Shioya Hospital; Shin-Oyama Municipal Hospital; and Utsunomiya Social Insurance Hospital, Tochigi, Japan).

We performed the baseline examination when the patient’s HF symptoms had improved and stabilized, and just before the patient left the hospital in most cases. Cardiologists saw all of the patients and made the diagnosis of HF. Both first-ever HF patients and recurrent HF patients were included in the present study. The exclusion criteria were as follows: informed consent for ambulatory BP monitoring (ABPM) not obtained; having an infection; documented dementia; delirium; depression during treatment; renal failure (serum creatinine >3 mg/dL); cancer; other severe non-cardiovascular diseases; and pacemaker or implanta ble cardioverter defibrillator implantation. We also excluded patients for whom any of the required data were lacking. This study was approved by the Institutional Review Board of the Jichi Medical University School of Medicine and the other 4 hospitals. We obtained informed consent from all participants.

History of hypertension was defined based on the patient’s medical records, self-report, or a history of antihypertensive medication use. Diabetes mellitus was defined as documented fasting glucose ≥126 mg/dL or random non-fasting glucose ≥200 mg/dL, or by the aforementioned criteria of glucose level documented on another date, or the use of either anti-diabetic drugs or insulin. We defined dyslipidemia as total cholesterol >240 mg/dL, triglyceride >150 mg/dL, or the use of an oral lipid-lowering drug. We calculated the estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease formula for Japanese patients: eGFR (mL/min/1.73 m^2)=194×(serum creatinine [mg/dL])^{−1.094}×(age [years])^{−0.287}×0.739 (if female). Body mass index (BMI) was calculated as weight/height^2 (kg/m^2).

Echocardiography
Transsthoracic 2-D echocardiography (Sonos 5500 and iE 33; Philips, Andover, MA, USA) was carried out in all patients. The interventricular septum (IVS), end-diastolic dimensions of the LV (LVDd), and posterior wall thickness (PWT) were measured in M-mode and occasionally in B-mode, in the parasternal long-axis view. LV mass (LVM) was calculated from IVS, LVDd, and PWT according to Devereux’s formula, and normalized to the patient’s body surface area to obtain the LVM index. LV ejection fraction (LVEF) was calculated using the Teichholz method. Relative wall thickness (RWT) was calculated as 2×(PWT/LVDd). HFpEF was defined as LVEF >50%, and HFrEF was defined as LVEF ≤50%.

Other Examinations
Blood was drawn after the patient rested for 10 min in the supine position. Brain-type natriuretic peptide (BNP) was measured from extracted plasma using highly sensitive, non-competitive immunoradiometric assays (Shiono-RIA; Shionogi, Osaka, Japan).

A pulse oximeter (PULSOX-M24, Konica Minolta, Osaka, Japan) was used to evaluate the nocturnal oxygen saturation change, which is a frequent comorbid condition in HF patients. Nocturnal pulse oximetry and ABPM were performed simultaneously in a hospital setting for all patients. The pulse oximeter was attached to the arm opposite the ABPM-attached arm (the ABPM device and pulse oximeter were not always placed on the same arms) just before the patient went to bed, and was removed after he or she woke up.

Oxygen desaturation per hour (i.e., oxygen desaturation index [ODI]) was used as an indicator of nocturnal intermittent hypoxia. A 3% ODI was selected as an index of oxygen desaturation, representing the number of events per hour of recording time in which the blood oxygen fell by >3%. Three percent ODI ≥5 had a sensitivity and specificity of 80% and 95%, respectively, for detecting an apnea-hypopnea index (AHI) ≥5 on polysomnography.

Mini-Mental State Examination (MMSE), a test of cognitive function, was carried out when the patient’s condition had improved and stabilized.

Follow-up and Outcomes
A follow-up study was performed from 1 October 2013 to 30 September 2015. The median follow-up period was 20.9 months. When the patients were followed up in the same hospital where they were treated, their medical records were reviewed. When the patients were followed in other hospitals, the medical records were analyzed via mail or telephone. The primary endpoint of this study was set as the composite outcome, which included all-cause mortality and cardiovascular events such as coronary events, HF.
Statistical Analysis

Data are expressed as mean±SD or percentage. One-way analysis of variance (ANOVA) was used to detect differences among the riser, non-dipper, and dipper subgroups in the HFpEF and HFrEF patients, and Tukey’s honestly significant difference test was performed between-group multiple pairwise comparisons of the means. Log-rank statistics were used to test the differences between Kaplan-Meier survival curves. Significant variables on univariate Cox regression analysis, such as BNP and sleep DBP in the HFpEF patients and BNP in the HFrEF patients, were included in a multivariable Cox regression analysis to examine the prognostic factors. Two-tailed P<0.05 was considered significant. All statistical analysis was performed with SPSS version 21.0 (IBM, Armonk, NY, USA).

Results

Baseline Characteristics

A total of 536 patients were enrolled, and 516 patients were
analyzed in the present study. Twenty patients were excluded due to incomplete data. Mean patient age was 69±13 years. A total of 62% of patients were male (n=321) and 38% were female (n=195). When HFpEF was defined as LVEF >50%, there were 182 patients with HFpEF and 334 patients with HFrEF. In the HFpEF patients, 53 (29.1%) had the riser BP pattern; in the HFrEF group 70 patients (21.0%) had the riser BP pattern.

Baseline characteristics in the HFpEF patients were similar between the risers, non-dippers and dippers except for a few items (Table 1). The percentage of history of hypertension was significantly higher in the risers and non-dippers than in the dippers (P=0.048). BNP was significantly higher in the risers than in the other 2 subgroups. Prevalence of 3% percent ODI ≥5 was significantly lower in the non-dippers than in the other subgroups. MMSE score was significantly lower in the risers than in the other subgroups. With regard to BP, 24-h SBP, sleep SBP, and sleep DBP were significantly higher in the risers than in the others (Table 2).

The baseline characteristics in the HFrEF patients were also similar between the 3 subgroups except for a few items. BNP was significantly higher in the risers and non-dippers than in the dippers. RWT was significantly higher in the risers than in the other subgroups. With regard to BP parameters, 24-h SBP, 24-h DBP, sleep SBP, and sleep DBP were significantly higher in the risers than in the other subgroups (Table 2).

Outcomes

There were a total of 220 composite outcomes during the follow-up period (Table 3). The incidence of events between the HFpEF and HFrEF patients was similar. On Kaplan-Meier analysis, the incidence of composite outcome was similar between the 2 groups (Figure 1). In the HFpEF patients, the risers had a significantly higher incidence of composite outcome than the dippers (P=0.03) on Kaplan-Meier analysis, whereas in the HFrEF patients, the incidence of composite outcome was similar between the 3 diurnal BP patterns (risers, non-dippers, dippers; Figure 2).

On univariate Cox regression analysis, BNP, sleep DBP, and the riser pattern were significant variables in the HFpEF group. On multivariate Cox regression analysis

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Table 2. Baseline Blood Pressure Parameters

|                  | HFpEF (n=182) | HFrEF (n=334) | P-value |
|------------------|--------------|--------------|---------|
|                  | Risers (n=53) | Non-dippers (n=70) | Dippers (n=59) | P-value |
| Casual SBP (mmHg) | 126±25       | 128±21       | 124±25   | 0.74    |
| Casual DBP (mmHg) | 68±16        | 70±11        | 70±13    | 0.72    |
| Casual PR (beats/min) | 70±14     | 71±15        | 73±13    | 0.50    |
| 24-h SBP (mmHg)   | 129±21††     | 122±20       | 118±16   | <0.01   |
| 24-h DBP (mmHg)   | 70±12        | 68±9         | 67±8     | 0.24    |
| 24-h PR (beats/min) | 66±10      | 66±11        | 69±11    | 0.23    |
| Awake SBP (mmHg)  | 127±21       | 126±16       | 124±17   | 0.75    |
| Awake DBP (mmHg)  | 70±11        | 70±9         | 71±9     | 0.83    |
| Awake PR (beats/min) | 67±10      | 67±11        | 70±11    | 0.20    |
| Sleep SBP (mmHg)  | 134±22**††   | 120±16       | 106±15   | <0.01   |
| Sleep DBP (mmHg)  | 72±13**††    | 66±9         | 61±9     | <0.01   |
| Sleep PR (beats/min) | 63±10      | 62±11        | 65±12    | 0.17    |

Data given as mean ± SD. *P<0.05 vs. non-dippers, **P<0.01 vs. non-dippers, †P<0.05 vs. dippers, ††P<0.01 vs. dippers. DBP, diastolic blood pressure; PR, pulse rate; SBP, systolic blood pressure. Other abbreviations as in Table 1.
Figure 2. Kaplan–Meier curve for composite outcome vs. diurnal blood pressure pattern. (A) Heart failure (HF) with preserved ejection fraction (EF; n=182); (B) HF with reduced EF (n=334).

Table 4. Indicators of Composite Outcome in HFrEF (n=182)

| Covariates                                      | Univariate                  | Multivariate                |
|-------------------------------------------------|-----------------------------|-----------------------------|
|                                                 | HR (95% CI) | P-value | HR (95% CI) | P-value |
| History of hypertension, Yes=1, No=0           | 1.55 (0.94–2.56) | 0.09     |             |         |
| BNP (pg/mL)†                                    | 1.46 (1.19–1.81) | <0.01    | 1.33 (1.06–1.66) | 0.01 |
| MMSE score                                      | 0.98 (0.94–1.03) | 0.43     |             |         |
| 3% ODI ≥5, Yes=1, No=0                         | 0.99 (0.63–1.60) | 0.99     |             |         |
| 24-h SBP (mmHg)                                 | 1.00 (0.98–1.01) | 0.41     |             |         |
| Sleep SBP (mmHg)                                | 1.00 (0.99–1.01) | 0.62     |             |         |
| Sleep DBP (mmHg)                                | 0.97 (0.95–0.99) | 0.01     | 0.96 (0.93–0.98) | <0.01 |
| Categorical variables                           | 0.08            | <0.01    |             |         |
| Dipper pattern                                  | 1 (Ref.)        |         | 1 (Ref.)    |         |
| Riser pattern                                   | 1.96 (1.09–3.56) | 0.03     | 3.01 (1.54–6.08) | <0.01 |
| Non-dipper pattern                              | 1.52 (0.86–2.67) | 0.15     | 1.98 (1.05–3.72) | 0.03 |

†Geometric mean. In univariate analysis, each variable was entered into the model 1 by 1. In multivariate analysis, all variables were entered into the model simultaneously. MMSE, Mini-Mental State Examination. Other abbreviations as in Tables 1, 2.

Table 5. Indicators of Composite Outcome in HFpEF (n=334)

| Covariates                                      | Univariate                  | Multivariate                |
|-------------------------------------------------|-----------------------------|-----------------------------|
|                                                 | HR (95% CI) | P-value | HR (95% CI) | P-value |
| BNP (pg/mL)†                                    | 1.67 (1.38–2.02) | <0.01    | 1.67 (1.37–2.02) | <0.01 |
| RWT                                             | 1.42 (0.34–5.99) | 0.63     |             |         |
| Office SBP (mmHg)                               | 1.00 (0.99–1.01) | 0.81     |             |         |
| 24-h SBP (mmHg)                                 | 1.00 (0.99–1.01) | 0.90     |             |         |
| 24-h DBP (mmHg)                                 | 0.98 (0.97–1.00) | 0.07     |             |         |
| Awake DBP (mmHg)                                | 0.98 (0.97–1.00) | 0.06     |             |         |
| Sleep SBP (mmHg)                                | 1.00 (0.99–1.01) | 0.98     |             |         |
| Sleep DBP (mmHg)                                | 0.99 (0.98–1.01) | 0.23     |             |         |
| Categorical variables                           | 0.54            | 0.92     |             |         |
| Dipper pattern                                  | 1 (Ref.)        |         | 1 (Ref.)    |         |
| Riser pattern                                   | 1.27 (0.75–2.15) | 0.37     | 1.10 (0.63–1.92) | 0.74 |
| Non-dipper pattern                              | 1.27 (0.82–1.98) | 0.29     | 1.10 (0.69–1.74) | 0.70 |

†Geometric mean. In univariate analysis, each variable was entered into the model 1 by 1. In multivariate analysis, all variables were entered into the model simultaneously. Abbreviations as in Tables 1, 2.
adjusting for BNP and sleep DBP, the riser pattern was a significant predictor for the incidence of composite outcome in the HFpEF group (hazard ratio [HR], 3.01, 95% CI: 1.54–6.08, P<0.01; Table 4). The non-dipper pattern was also significant (HR 1.98, 95% CI: 1.05–3.72, P=0.03).

In the HFrEF group, BNP was significant on univariate Cox regression analysis. On multivariate Cox regression analysis adjusted for BNP, the categorical variables of diurnal BP patterns were not predictors of the incidence of the composite outcome (Table 5), but BNP was a significant predictor of composite outcome (HR, 1.67; 95% CI: 1.37–2.02, P<0.01). When we combined the non-dippers and risers as non-dippers (night/day SBP >0.9), the non-dippers had a significantly higher incidence of composite outcome than the dippers in the HFpEF group on Kaplan-Meier analysis (P=0.046; Figure S1). On multivariate Cox regression analysis adjusted for significant covariates, the non-dipper pattern was a significant predictor of composite outcome in the HFpEF group (HR, 2.30; 95% CI: 1.28–4.14, P<0.01; Table S1). In the HFrEF patients, no such differences were observed. On multivariate Cox regression analysis adjusted for significant covariates, the non-dipper pattern was not a significant predictor of composite outcome (Table S2).

Discussion

This study involved a cohort of hospitalized HF patients with ABPM. In our previous report, we noted a significant association between HFpEF and the riser BP pattern. To our knowledge, the present study is the first to demonstrate that abnormal circadian BP rhythm is a significant predictor of composite outcome in HFpEF patients. In the present HFpEF group, the HF patients with the riser BP pattern had a 3-fold higher risk of composite outcome compared with the dipper patients, but this relationship was not seen in the HFrEF group.

In the present study, the riser BP pattern was a significant predictor of composite outcome in the HFpEF group, but not in the HFrEF patients. One possible reason for this is a fluid volume shift from the peripheral extremities to the heart during sleep. In the supine position, the venous return to the heart increases and the ventricular volume increases. According to Laplace’s law, ventricular wall pressure would elevate with increasing ventricular volume. The LV diastolic dysfunction and increased LV stiffness in HFpEF patients, however, means that they cannot tolerate the increased LV volume and pressure. These pathophysiological conditions may cause acute decompensated HF events, such as the acute pulmonary edema frequently seen during sleep in HFpEF patients.

In the present study, we investigated the relationships between HF onset time and circadian BP rhythm. The distributions of HF event onset time were similar among the risers, non-dippers, and dippers, regardless of whether the patients had HFpEF or HFrEF. We could not, however, evaluate circadian BP rhythm at the onset times. There are few reports of admission time in acute HF, but these reports showed that SBP on admission was higher in the HF patients with night admission. Although circadian BP rhythm was not investigated in those reports, nocturnal BP elevation could be a indicator of worsening HF at night.

A second possible explanation for the aforementioned difference between the present HFpEF and HFrEF patients is that the circadian BP pattern has a differential impact on outcome between HFpEF and HFrEF. This discrepancy could be explained by the following mechanisms. Hypertension-related subclinical organ damage (such as LV hypertrophy and chronic kidney disease) are more advanced in HFpEF patients than in HFrEF patients. In the present study, HFpEF patients with the riser BP pattern had lower eGFR and higher RWT than the HFrEF riser BP patients. These types of subclinical organ damage could be further enhanced by the riser BP pattern, and lead to a further cardiovascular event.

In the present study, the HFpEF patients with the riser BP pattern were older, had a higher prevalence of hypertension, and had lower MMSE score than the HFrEF patients. These conditions were not due to age. We showed previously that the riser BP pattern was significantly associated with MMSE score after adjusting for age in HF patients. Therefore, the riser BP pattern could be a comprehensive marker of subclinical organ damage in HFpEF patients, suggesting that a significant association between riser BP pattern and subclinical organ damage may exist independently of age.

Taken all of the current findings into account, there are some therapeutic implications for the improvement of outcome in HFpEF patients with the riser pattern. In the present patients, the frequency of antihypertensive drug use was similar between the risers, non-dippers, and dippers. In addition, the use of antihypertensive drugs such as angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), β-blockers, calcium channel blockers, and diuretics was not significantly associated with outcome in the HFpEF patients. In the HFpEF patients with the riser BP pattern, however, ACEI use was significantly associated with outcome (HR 0.54; 95% CI: 0.31–0.94, P=0.03), but other drugs were not. At the present time there are no medications to improve outcome in HFpEF. ACEI could be effective to inhibit the renin-angiotensin system during the night when elevated nocturnal BP is observed, but there are apparently no reports on the effect of ACEI on circadian BP rhythm in HFpEF patients with the riser BP pattern.

The prognosis of HFrEF was not associated with circadian BP rhythm in the present study. This is not consistent with the previous report in which the riser BP pattern was associated with adverse outcome in HFrEF. This difference can be explained by the difference in HF severity. The percentage of NYHA III/IV HF patients in that study was greater than in the present study. Abnormal circadian BP rhythm could have a strong effect on HFpEF patients with severe symptoms, and result in poor outcome.

The strength of the present study is that the sample number was relatively large for a study of ABPM in hospitalized HF patients. There are some limitations in this study. First, ABPM was performed during hospitalization, although ABPM in a hospital setting may not always represent normal daily life and sleep habits. Earlier studies, however, showed that ABPM had prognostic significance even during hospitalization. Second, the dose of antihypertensive medications and the timing of the drug treatment could influence diurnal BP pattern, but multiple drugs are usually prescribed in HF patients. Third, the present definition of HFpEF was LVEF >50%, although the cut-off of LVEF to define HFpEF was not established. We used various cut-offs of LVEF to define HFpEF: LVEF 40%, LVEF 45%, and LVEF 50%, for which the present results were significant.
Therefore, the LVEF cut-off of 50% was adopted for the definition of HfPEF.

Conclusions
An abnormal pattern of circadian BP rhythm known as the riser pattern was a novel predictor of cardiovascular outcome in patients with HfPEF. Sleep BP could be a therapeutic target for better outcome in HfPEF patients.

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Disclosures
The authors declare no conflict of interest.

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Supplementary Files
Supplementary File 1
Figure S1. Kaplan-Meier curve for composite outcome in dippers vs. non-dippers.
Table S1. Indicators of composite outcome in HfPEF (n=182)
Table S2. Indicators of composite outcome in HfPEF (n=334)