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ORIGINAL RESEARCH ARTICLE

Differences in blood pressure riser pattern in patients with acute heart failure with reduced mid-range and preserved ejection fraction

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Abstract

Aims Heart failure (HF) is classified into three types according to left ventricular ejection fraction (EF). The effect of blood pressure (BP) on the pathogenesis of each type is assumed to be different. However, the association between the prognosis of each type of HF and abnormal BP variations assessed by ambulatory BP monitoring (ABPM), such as nocturnal hypertension and the riser pattern, remains unclear.

Methods and results We studied 325 consecutive patients with decompensated HF who were acutely admitted to our hospital and underwent ABPM at discharge. During a mean follow-up of 30.0 months, 52 cardiovascular and 112 all-cause deaths occurred. The Cox proportional hazards model showed that the mean values of 24 h, awake, and sleep-time systolic BP (SBP), and abnormal 24 h ABPM patterns, such as nocturnal hypertension and non-dipper pattern, were not associated with either all-cause or cardiovascular mortality in patients with HF with reduced EF (HFrEF), HF with mid-range EF (HFmrEF), or HF with preserved EF (HFpEF), except for sleep-time SBP in HFrEF. However, the riser pattern was a significant and independent predictor of all-cause and cardiovascular deaths in patients with HFpEF (hazard ratio, 2.01; 95% confidence interval, 1.12–3.62; 0.0200; and hazard ratio, 2.48; 95% confidence interval, 1.08–5.90; 0.0332, respectively). Sleep-time pulse rate was similarly decreased in both the riser and non-riser groups.

Conclusions The riser pattern of SBP was associated with an increased risk of adverse outcomes among patients with HFpEF but not HFrEF or HFmrEF.

Keywords Ambulatory blood pressure monitoring; Riser pattern; Heart failure with preserved ejection fraction; Heart failure with mid-range ejection fraction; Heart failure with reduced ejection fraction

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Introduction

Heart failure (HF) is a major public health issue worldwide. Recent guidelines on acute and chronic HF classified them into three groups according to left ventricular ejection fraction (LVEF): HF with reduced EF (HFrEF; EF $<$40%), HF with mid-range EF (HFmrEF; 40% $\leq$ EF $<$ 50%), and HF with preserved EF (HFpEF; 50% $\leq$ EF). Although treatment strategies for HFrEF have significantly improved over the past two decades,[1–3] its prognosis remains poor. As well, previous randomized clinical trials in patients with HFpEF have failed to show a beneficial effect of the drug therapy being trialled. Of note, patients with HFmrEF were not included in some of these earlier clinical trials.

To further improve the treatment strategy for all types of HF, the treatable risk factors for HF should be investigated. Although hypertension is one of the well-known major risk factors for the development of HF, once HF develops, the relationship between systolic blood pressure (SBP) and the recurrence of HF is unclear. Several earlier studies have reported that lower SBP at admission is associated with a higher incidence rate of cardiovascular events, including unexpected HF admission.[4–6] However, none of the guidelines for the management of hypertension or HF have provided a target SBP for any of the HF types.

Ambulatory BP monitoring (ABPM) is a useful tool to investigate the circadian rhythm of BP in individuals on no medication and to assess the effect of antihypertensive drugs on 24 h BP control in patients undergoing treatment. Recently, serial out-of-office ABPM was recommended for better management of hypertension.[7] ABPM can also provide novel information on risk factors for cardiovascular death and HF. Several earlier reports showed that abnormal variations in the 24 h BP, such as the morning surge and nocturnal increase in SBP, are important predictors of cardiovascular events in the general population and in patients with hypertension, irrespective of BP treatment.[8–13] However, there have been only a few reports on ABPM measurements in patients with HF.[14–16] Recently, Komori *et al*.[16] reported that the riser pattern of SBP is associated with worse prognosis among patients with HFpEF but not those with HFrEF. In this study, however, HFrEF was defined as EF ≤50%, which includes HFrEF (EF <40%) and HFmrEF (40% ≤ EF < 50%). Considering the limitation of current evidence regarding the relationship between BP and the three types of HF, our aim in this study was to investigated the prognostic impact of 24 h BP variation for the three types of HF (HFrEF, HFmrEF, and HFpEF), using the data from the Nara Registry and Analyses for Heart Failure cohort study (NARA-HF study).[17–22]

Methods

Study population and data collection

The NARA-HF was designed as a dynamic cohort study.[17–22] The study recruited 1074 consecutive patients who were emergently admitted to our department or the coronary care unit at our hospital with documented acute decompensated HF (ADHF; either acute new-onset or acute-on-chronic HF) between January 2007 and December 2016. The diagnosis of HF was based on the Framingham Criteria.[23] The study population included patients with HFrEF, HFmrEF, and HFpEF. Patients with acute myocardial infarction, acute myocarditis, and acute HF with acute pulmonary embolism were excluded.

The ABPM measurements started in April 2011 as part of the NARA-HF study, and 369 of 1074 patients had ABPM performed immediately before discharge. Among them, 44 patients were excluded from the analysis because of insufficient data. Consequently, we analysed the data of 325 patients (124 with HFrEF, 71 with HFmrEF, and 130 with HFpEF). For each patient, baseline data collected included age, sex, body mass index (BMI), HF aetiology, medical history, vital signs, laboratory and echocardiographic data, and medications on admission and at discharge.

The study was approved by the Ethics Committee of Nara Medical University, and written informed consent was obtained from all patients in accordance with the Declaration of Helsinki's Ethical Principles for Medical Research Involving Human Subjects.

Blood pressure measurement

Ambulatory blood pressure monitoring was performed immediately before discharge by an automatic system using electrical cuff inflation (FB-270; Fukuda Denshi Co., Tokyo, Japan), which recorded SBP and diastolic BP (DBP) (by the oscillometric method) and pulse rate every 30 min during daytime (6 a.m. to 9:59 p.m.) and every 60 min during night-time (10 p.m. to 5:59 a.m.). BP measurements were expressed in millimetres of mercury (mmHg). BP measurement was performed on the side opposite the dominant arm in this study.

The 24 h BP was defined as the average value of BP measured over an entire day. We defined the awake BP as the average value of BP measurements from 7 a.m. to 8:30 p.m. and the sleep-time BP as the average value of BP measurements from 10 p.m. to 5 a.m., as awake-time was 6 a.m. and lights-out time was 9 p.m. at our hospital. A minimum of 20 valid awake readings and five valid sleep readings were made to define the awake and sleep-time BP, but all patients had significantly more valid readings. Nocturnal hypertension was defined as a sleep-time SBP ≥120 mmHg and/or sleep-time DBP ≥70 mmHg, based on the 2014 guidelines for the management of hypertension published by The Japanese Society of Hypertension.[7] The nocturnal BP fall (%) was calculated as (awake SBP − sleep-time SBP)/awake SBP. We classified the patients' nocturnal BP fall into the following three patterns: the dipper pattern, if the nocturnal BP fall was higher than 10%; the non-dipper pattern, if it was between 0% and 10%; and the riser pattern, if it was <0%. Patients with an extreme dipper pattern (nocturnal BP fall higher than 20%) were combined with those having the dipper pattern for analysis due to the limited number of cases (n = 8).

Outcomes

The primary endpoints were all-cause and cardiovascular mortality. Cardiovascular death was defined as death due to HF, myocardial infarction, sudden death, stroke, and vascular disease such as aortic dissection. We checked medical records to determine the vital status and the cause of death. When this information was unavailable in the medical records, we telephoned the patients or their families.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median (interquartile range), and inter-group differences were compared using Student's *t*-test. Categorical variables were summarized as percentages and analysed using the χ^2 test. A Cox proportional hazards model was used to investigate the hazard ratio (HR) for all-cause and cardiovascular deaths. Results were reported as HR, 95% confidence interval (CI), and *P* values. The HR for outcomes in the riser group was compared with that for the non-riser group, which served as the reference group. JMP version 12 for Windows (SAS Institute Inc., Cary, NC) was used for all statistical analyses. *P* values <0.05 were considered statistically significant.

Results

Baseline characteristics in patients with heart failure with reduced ejection fraction, heart failure with mid-range ejection fraction, and heart failure with preserved ejection fraction

The mean age of all patients with HF registered in the NARA-HF 3 study was 73.4 ± 12.3 years, and the proportion of female patients was 42.3%. As in previous reports, the proportion of elderly and female patients was as follows: HFpEF $>$ HFmrEF $>$ HFrEF (Supporting Information, *Table S1*). To investigate the differences in ABPM measurements between HFrEF, HFmrEF, and HFpEF, we studied 325 patients who underwent ABPM at discharge. We classified the 325 patients with HF into HFrEF, HFmrEF, and HFpEF groups based on their LVEF and compared their baseline clinical characteristics (Supporting Information, *Table S2*). The age was younger in the HFrEF group than in the HFmrEF and HFpEF group. The proportion of female patients was higher in the HFpEF group than in the HFrEF group, with the HFmrEF group falling in between. BMI was similar among the three groups. In terms of their echocardiographic data, the LV end-diastolic diameter and LVEF in the HFmrEF group was also in between the values in the HFrEF and HFpEF groups. Haemoglobin levels was higher in the HFrEF group than in the HFmrEF and HFpEF groups, although sodium was higher and brain natriuretic peptide (BNP) level was lower in the HFpEF group than in the HFmrEF and HFrEF groups. The estimated glomerular filtration rate (eGFR) was higher in the HFrEF group than in the HFpEF group, with the HFmrEF group as the intermediate. The prescription rate of angiotensin-converting enzyme inhibitors (ACEis)/angiotensin receptor blockers (ARBs), beta-blockers, mineral corticoid receptor antagonists, and diuretics at discharge was higher in the HFrEF group than in the HFpEF group, although the prescription rate of calcium blockers was lower. The rate of the prescription of all drugs for the HFmrEF group was between that of the HFrEF and HFpEF groups.

Differences in vital signs and ambulatory blood pressure monitoring among the heart failure with reduced ejection fraction, heart failure with mid-range ejection fraction, and heart failure with reduced ejection fraction groups

Table 1 presents the vital signs and ABPM data of all three groups. At discharge, patients with HFpEF had a significantly higher SBP compared with patients with HFrEF, and patients with HFmrEF were intermediate. However, the DBP and pulse rate at discharge were similar among the three groups.

With regard to ABPM, the mean 24 h, awake, and sleep-time SBPs were significantly higher in the HFpEF group than in the HFrEF group, and all SBP measurements in the HFmrEF group were intermediate. In contrast, there was no significant between-group difference with regard to mean DBP and pulse rate. With respect to the pattern of circadian rhythm, the proportion of patterns was similar among the three groups. The incidence of nocturnal hypertension was higher among patients in the HFpEF group than in the HFrEF group, and that in the HFmrEF group was intermediate.

Prognosis for all patients with acute decompensated heart failure

During the mean follow-up period of 30.0 months, 112 (34.5%) of all patients with ADHF died, 52 (16.0%) of whom were caused by cardiovascular death. We constructed a univariate Cox proportional hazards model to investigate the HR for all-cause death among all patients. None of the average SBPs measurements in all categories (24 h, awake, and sleep-time) were related to all-cause or cardiovascular death. Moreover, neither nocturnal hypertension nor the circadian rhythm pattern was related to all-cause or cardiovascular death (*Figure 1A*).

Differences in prognosis among patients with heart failure with preserved ejection fraction, heart failure with mid-range ejection fraction, and heart failure with reduced ejection fraction

Subsequently, we compared the HR for all-cause death in the HFpEF, HFmrEF, and HFrEF groups (*Figure 1B*). The mean

Table 1 Vital signs and ABPM in the HFpEF, HFmrEF, and HFrEF groups

Characteristic	HFpEF (n = 130)	HFmrEF (n = 71)	HFrEF (n = 124)	P value
Vital signs on admission				
SBP, mmHg	156.9 ± 39.9	153.0 ± 30.7	141.1 ± 34.0	0.0032
DBP, mmHg	85.1 ± 26.8	90.1 ± 21.2	87.2 ± 26.6	0.2614
Pulse rate, b.p.m.	96.2 ± 29.0	104.9 ± 26.9	105.7 ± 25.5	0.0034
Vital signs at discharge				
SBP, mmHg	116.7 ± 18.1	112.8 ± 17.0	105.1 ± 13.6	<0.0001
DBP, mmHg	62.2 ± 10.1	61.2 ± 9.5	62.2 ± 10.5	0.7801
Pulse rate, b.p.m.	70.9 ± 12.0	68.8 ± 10.7	71.6 ± 10.8	0.2144
ABPM				
The average SBP, mmHg				
24 h (0:00–24:00)	118.1 ± 18.1	111.5 ± 16.3	101.9 ± 14.1	<0.0001
Awake (7:00–20:30)	118.8 ± 17.7	112.0 ± 16.7	102.6 ± 14.1	<0.0001
Sleep-time (22:00–5:00)	115.6 ± 21.4	109.6 ± 16.9	99.8 ± 16.5	<0.0001
The average pulse rate, b.p.m.				
24 h (0:00–24:00)	69.0 ± 8.9	70.5 ± 10.3	70.7 ± 8.3	0.2951
Awake (7:00–20:30)	69.9 ± 8.9	71.6 ± 9.9	72.0 ± 8.8	0.2203
Sleep-time (22:00–5:00)	66.5 ± 12.4	68.3 ± 14.3	66.8 ± 10.3	0.8533
Pattern of circadian rhythm, %				
Riser pattern	21.5	18.3	14.5	0.3451
Non-dipper pattern	40.0	43.7	52.4	0.1301
Dipper pattern	38.5	38.0	33.1	0.6310
Nocturnal hypertension, %	43.1	33.8	26.6	0.0217

ABPM, ambulatory blood pressure monitoring; DBP, diastolic blood pressure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; SBP, systolic blood pressure.

SBPs in any category, except for night-time in the HFrEF group, were not associated with all-cause death. Nocturnal hypertension or non-dipper patterns were also not related to all-cause death in all groups. However, in the HFpEF group, the riser pattern was associated with all-cause death but not in the HFrEF and HFmrEF groups. Similar results were observed with regard to cardiovascular death.

Comparison between the riser and non-riser patterns

To further investigate the impact of the riser pattern on the prognosis of patients with ADHF, we divided patients in the HFpEF, HFmrEF, and HFrEF groups into two subgroups, according to their riser or non-riser pattern (which includes the non-dipper and dipper patterns).

We compared the baseline clinical characteristics between the riser and non-riser groups (*Table 2*). Age, BMI, the proportion of female patients, and the cause of HF were similar between the two groups across all HF types. The proportions of clinical scenarios were equal between the two groups in all HF types. In terms of laboratory data at discharge, haemoglobin, eGFR, sodium, and BNP levels were similar in the two groups. With regard to antihypertensive drugs at discharge, the proportions of patients treated with ACEis/ARBs, beta-blockers, diuretics, or calcium blockers were similar in the two groups across all HF types. In the HFpEF group, mineral corticoid receptor antagonists were more frequently administered in the non-riser group than in the riser group.

The differences in ambulatory blood pressure monitoring between the riser and non-riser patterns

Figure 2 and *Table 3* show the BP profiles during the 24 h of ABPM in the HFpEF, HFmrEF, and HFrEF groups. Sleep-time SBP was significantly higher in the riser group than in the non-riser group across all HF types. The elevation of sleep-time SBP was significantly higher among patients in the HFpEF group than either in the HFrEF or HFmrEF groups. However, the sleep-time pulse rate was similarly decreased in both the riser and non-riser groups across all HF types. Consequently, the sleep-time pulse rate in the riser group was similar to that in the non-riser group among all patients with HF.

Prognosis and outcome

Figure 3 shows the Kaplan–Meier survival curves for the HFpEF, HFmrEF, and HFrEF groups. With regard to the HFpEF group, the survival rate was significantly lower in the riser group than in the non-riser group, for all-cause death (log-rank 0.0159; *Figure 3A*) and cardiovascular death (log-rank 0.0172; *Figure 3B*). In contrast, both all-cause and cardiovascular deaths were similar between the riser group and the non-riser group in patients with HFmrEF (log-rank 0.7773 and log-rank 0.2175; *Figure 3C, D*) and patients with HFrEF (log-rank 0.8145 and log-rank 0.4147; *Figure 3E, F*).

Figure 1 (A) Univariate HRs (95% CI) for all-cause death in all patients. The black squares indicate the HRs for all-cause death. The solid lines indicate the 95% CI. (B) Univariate HRs (95% CI) for all-cause death in the HFpEF, HFmrEF, and HFrEF groups. The black rectangles, white triangles, and black diamonds indicate the HRs for all-cause death in the HFpEF, HFmrEF, and HFrEF groups, respectively. Solid lines indicate the 95% CI. CI, confidence interval; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; SBP, systolic blood pressure.

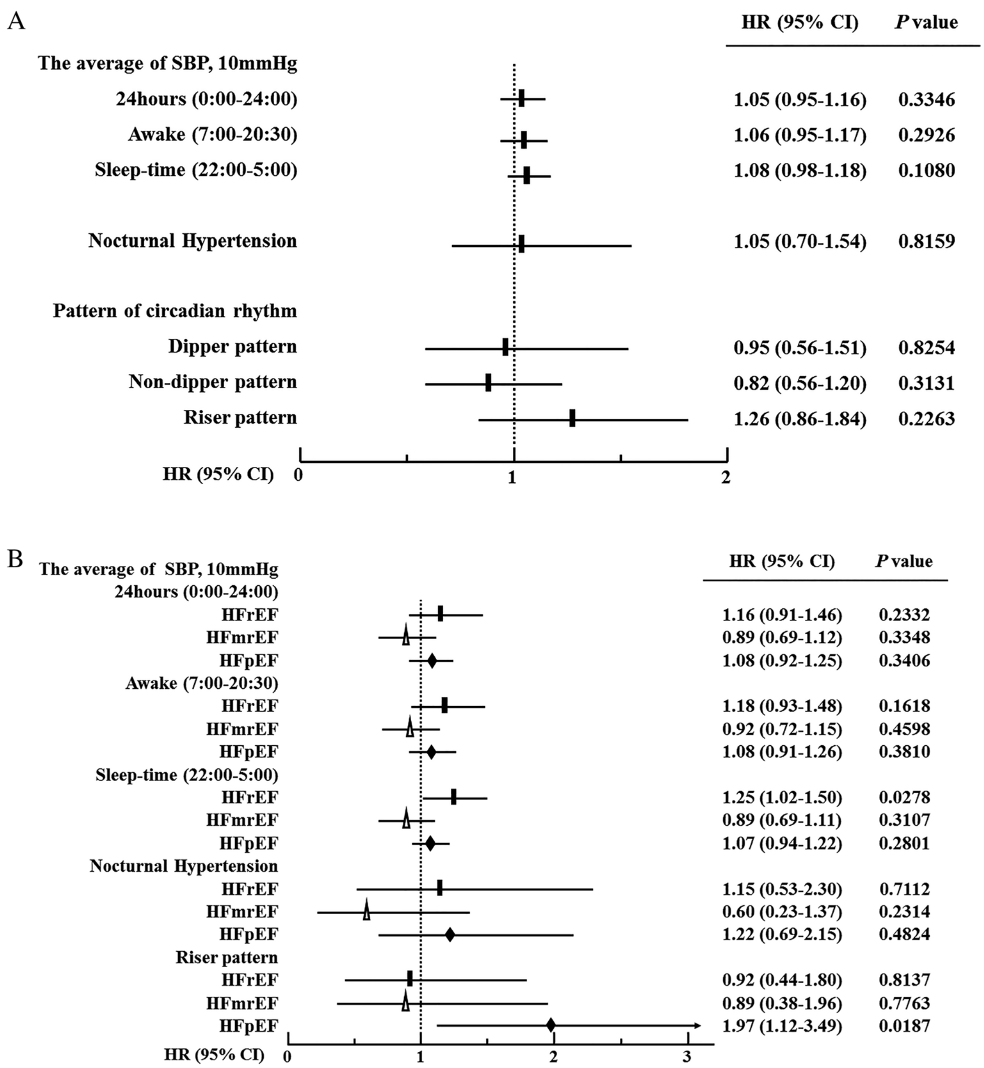


Table 4 shows the unadjusted and adjusted HRs of outcomes for the riser and non-riser groups. Among patients in the HFpEF group, the unadjusted HRs for all-cause and cardiovascular deaths were significantly higher in the riser group than in the non-riser group (HR, 1.97; 95% CI, 1.12–3.49; 0.0187; and HR, 2.60; 95% CI, 1.16–6.06; 0.0206, respectively). Even after adjustment for covariates (age, haemoglobin, eGFR, and BNP at discharge) in the multivariable Cox proportional hazards model, the riser pattern among patients in the HFpEF group remained an independent predictor of all-cause and cardiovascular deaths (HR, 2.01; 95% CI, 1.12–3.62; 0.0200; and HR, 2.48; 95% CI, 1.08–5.90; 0.0332, respectively).

Discussion

The present study investigated the 24 h profile of BP and pulse rate in patients with ADHF and demonstrated that the riser pattern is associated with both all-cause and cardiovascular deaths only in patients with HFpEF but not in those with HFrEF or HFmrEF. The clinical significance of the riser pattern among patients with HFmrEF is closer to that of patients with HFrEF than those of patients with HFpEF, although most baseline characteristics for patients with HFmrEF fall between those for patients with HFrEF and HFpEF.

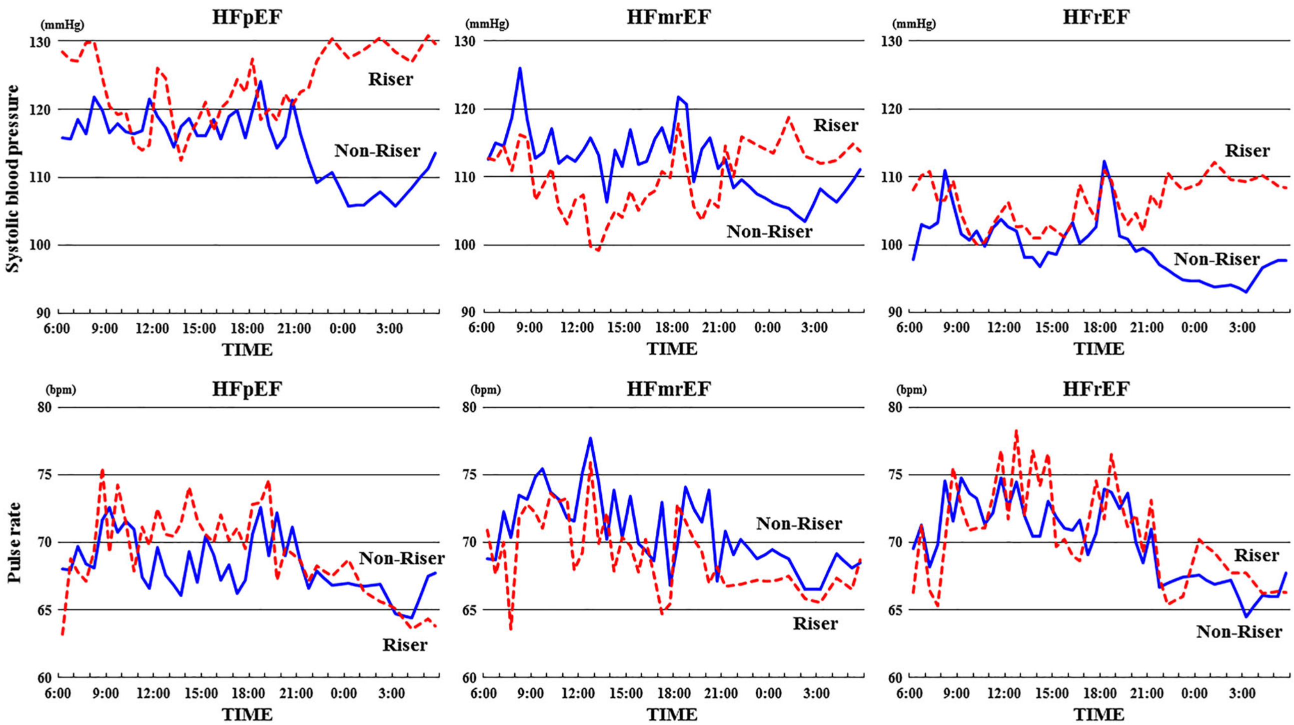
Table 2 Baseline characteristics in the riser and non-riser groups

Characteristic	HFpEF Non-riser (n = 80)	HFpEF Riser (n = 50)	HFpEF P value	HFmrEF Non-riser (n = 44)	HFmrEF Riser (n = 27)	HFmrEF P value	HFrEF Non-riser (n = 83)	HFrEF Riser (n = 41)	HFrEF P value
Demographic									
Age, years	75.7 ± 11.0	75.9 ± 11.8	0.8368	75.5 ± 11.3	76.6 ± 10.5	0.7355	71.4 ± 12.7	69.0 ± 12.3	0.2542
Female, %	58.8	50.0	0.3292	50.0	33.3	0.1665	26.5	31.7	0.5472
BMI, kg/m^2	23.3 ± 3.4	23.6 ± 4.2	0.6677	22.0 ± 3.4	23.6 ± 4.2	0.6677	23.1 ± 3.1	24.1 ± 4.4	0.1221
Cause of HF, %									
Ischaemic	23.8	22.0	0.8174	65.9	51.9	0.2406	43.4	36.6	0.4684
Valvular	13.8	18.0	0.5166	11.4	11.1	0.9739	8.4	4.9	0.4585
Dilated cardiomyopathy	6.3	4.0	0.5729	15.9	18.5	0.7768	36.1	41.5	0.5668
Medical history, %									
Hypertension	77.5	86.0	0.2236	72.7	69.2	0.7550	74.1	85.4	0.1452
Diabetes mellitus	41.8	42.0	0.9796	52.3	40.7	0.3440	38.3	43.9	0.5498
Dyslipidaemia	37.3	48.0	0.2365	53.7	56.0	0.8529	40.0	31.7	0.3688
Smoking	16.3	22.0	0.4145	39.5	25.9	0.2381	31.7	27.5	0.6334
Old myocardial infarction	22.5	12.0	0.1241	45.5	29.6	0.1815	34.6	26.8	0.3827
Clinical scenario (CS), %			0.1701			0.3329			0.3191
CS1	62.5	74.0		63.6	55.6		44.6	56.1	
CS2	28.8	24.0		36.4	40.7		45.8	31.7	
CS3	8.8	2.0		0.0	3.7		9.6	12.2	
NYHA class on admission, %									
III or IV	90.0	84.0	0.3167	88.6	100	0.0251	90.4	90.2	0.9834
Echocardiographic parameters									
LVEF, %	63.5 ± 8.2	63.1 ± 6.8	0.7033	44.6 ± 2.9	44.7 ± 2.5	0.9430	29.4 ± 6.8	30.1 ± 6.7	0.5389
LVEDD, mm	46.4 ± 6.4	47.3 ± 6.0	0.6175	52.6 ± 6.8	53.1 ± 7.1	0.8708	59.7 ± 9.4	62.3 ± 8.7	0.3405
Laboratory data at discharge									
Haemoglobin, g/dL	11.3 ± 1.9	11.0 ± 1.9	0.2751	11.2 ± 1.7	11.1 ± 1.7	0.6826	12.3 ± 2.0	12.7 ± 2.4	0.3650
eGFR, mL/min/1.73m^2	40.7 ± 23.2	36.1 ± 22.6	0.3115	45.2 ± 18.9	40.6 ± 15.9	0.3255	47.2 ± 23.2	49.2 ± 27.0	0.8776
Sodium, mmol/L	138.0 ± 3.5	138.8 ± 3.6	0.0993	136.9 ± 3.2	138.0 ± 3.6	0.3467	137.5 ± 3.7	137.8 ± 3.1	0.8259
Plasma BNP, pg/mL[a]	196 (113–377)	183 (114–345)	0.9765	322 (104–574)	335 (199–697)	0.2469	288 (178–539)	327 (209–513)	0.9498
Medication at discharge, %									
ACEi or ARBs	77.5	80.0	0.7350	88.4	85.2	0.7002	92.7	97.6	0.2384
MRAs	37.5	18.0	0.0157	32.6	33.3	0.9464	47.7	51.2	0.7020
Beta-blockers	61.3	62.0	0.9318	81.4	74.1	0.4707	90.2	92.7	0.6500
Ca channel blockers	41.8	56.0	0.1145	19.1	22.2	0.7499	7.4	2.4	0.2326
Diuretics	83.8	76.0	0.2797	79.1	92.6	0.1134	89.0	85.4	0.5638

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; beta-blocker, beta-adrenergic receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; Ca, calcium; EDD, end-diastolic diameter; EF ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure reduced with ejection fraction; LV, left ventricular; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PRA, plasma renin activity.

[a]Data are shown as percentages, means ± standard deviation, or medians (25th and 75th percentile).

Figure 2 The SBP and pulse rate profiles over 24 h of ABPM in the HFpEF, HFmrEF, and HFrEF groups. The dotted line is the riser pattern, and the solid line is the non-riser pattern. CI, confidence interval; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; SBP, systolic blood pressure.



In earlier studies, high SBP was found to be a predictor of better prognosis among patients with HFrEF and HFpEF.[24,25] However, our study failed to show an association between average values of 24 h or awake-time SBP and better outcomes for any type of HF. In the NARA-HF 3 study, SBP higher than 100 mmHg at discharge was also a predictor of better outcomes among patients with HFrEF but not among those with HFmrEF or HFpEF (data not shown). More interestingly, abnormal 24 h variations of SBP, such as nocturnal hypertension or non-dipper pattern, which are associated with cardiovascular events among patients with hypertension irrespective of whether they were being treated with antihypertensive drugs[26–28], were not observed in any of the groups in our study. This indicates that the clinical significance of 24 h BP variation is different between patients with hypertension and those with HF.

The riser pattern was associated with all-cause and cardiovascular deaths only among patients with HFpEF. This finding is consistent with the earlier report by Komori *et al.*,[16] in which patients with HF were divided into two groups of patients, HFrEF and HFpEF, and patients with HFmrEF were included in the same group as patients with HFrEF. In accordance with their findings, our results showed that the riser pattern was not associated with outcomes among patients with either HFrEF or HFmrEF. Although the mechanism underlying the association between the riser pattern and a prognosis among patients with HFpEF is currently unclear, it may be related to the fact that hypertension is more closely involved in the aetiology of HFpEF than HFrEF. Because all patients in the current study were receiving medical therapy, the mechanism of the development of the riser pattern should be interpreted with caution. In short, our results could be indicative that sleep-time SBP is simply not well controlled by the treatment or that the intrinsic pathophysiology of HFpEF is possibly related to the development of the riser pattern. Nevertheless, the pathology of HFpEF is different from that of HFrEF and probably from that of HFmrEF as well.

Although the mechanism of the development of the riser pattern has not been clearly understood yet, it has been suggested that the disturbances in the sympathetic nervous system, the baroreceptor reflex, and volume overload are involved in its development during sleep.[12] Generally, the changes in pulse rate are also well correlated with the activation of the sympathetic nervous system. However, in this study, the sleep-time pulse rate was similarly decreased in both the riser and non-riser groups across all types of HFs, indicative of a decrease in sympathetic nervous activity during sleep in both the riser and non-riser groups. Therefore, it may be possible that the riser pattern results from a volume overload than being related to sympathetic nervous activity. Considering that the pulse rate in patients with hypertension and the riser pattern is also lower during sleep-time than

Table 3 Vital signs at discharge and ABPM in the riser and non-riser groups

Characteristic	HFpEF			HFmrEF			HFrEF		
	Non-riser (*n* = 80)	Riser (*n* = 50)	*P* value	Non-riser (*n* = 44)	Riser (*n* = 27)	*P* value	Non-riser (*n* = 83)	Riser (*n* = 41)	*P* value
Vital signs on admission									
SBP, mmHg	154.2 ± 41.0	161.1 ± 38.1	0.3549	154.8 ± 30.8	150.3 ± 30.8	0.4957	140.3 ± 35.2	142.8 ± 31.7	0.5662
DBP, mmHg	83.6 ± 25.3	87.5 ± 29.1	0.5092	91.7 ± 20.4	87.5 ± 22.6	0.3522	86.9 ± 28.7	87.9 ± 21.9	0.5412
Pulse rate, b.p.m.	95.4 ± 28.6	97.5 ± 29.9	0.4481	107.3 ± 27.3	101.0 ± 26.3	0.5339	104.6 ± 23.8	108.0 ± 28.8	0.9259
Vital signs at discharge									
SBP, mmHg	115.0 ± 17.5	119.4 ± 18.8	0.2435	114.3 ± 17.9	110.2 ± 15.4	0.3370	105.2 ± 13.8	105.0 ± 13.4	0.7249
DBP, mmHg	61.1 ± 9.2	64.1 ± 11.3	0.1046	61.8 ± 9.9	60.3 ± 9.0	0.4091	62.1 ± 10.6	62.4 ± 10.4	0.9336
Pulse rate, b.p.m.	69.5 ± 12.2	73.2 ± 11.5	0.0359	69.0 ± 11.2	68.4 ± 10.1	0.8122	72.3 ± 11.5	70.2 ± 9.1	0.3958
ABPM									
Average SBP, mmHg									
24 h (0:00–24:00)	115.4 ± 17.8	122.5 ± 17.8	0.0171	112.8 ± 17.5	109.3 ± 14.2	0.4344	100.2 ± 13.7	105.4 ± 14.5	0.0422
Awake (7:00–20:30)	117.8 ± 18.2	120.3 ± 16.8	0.2935	114.8 ± 17.8	107.5 ± 14.0	0.0903	102.0 ± 14.2	103.8 ± 14.1	0.4966
Sleep-time (22:00–5:00)	107.6 ± 17.9	128.4 ± 20.4	<0.0001	106.8 ± 17.5	114.2 ± 15.0	0.0460	94.9 ± 13.8	109.9 ± 17.1	<0.0001
Average pulse rate, b.p.m.									
24 h (0:00–24:00)	68.6 ± 9.3	69.6 ± 8.3	0.4833	71.4 ± 10.2	69.1 ± 10.6	0.4379	70.6 ± 7.5	70.8 ± 9.8	0.9091
Awake (7:00–20:30)	69.3 ± 9.3	71.0 ± 8.2	0.2056	72.6 ± 9.5	70.0 ± 10.5	0.1653	72.0 ± 7.9	72.0 ± 10.5	0.8442
Sleep-time (22:00–5:00)	66.5 ± 12.7	66.5 ± 12.0	0.9962	69.2 ± 15.7	66.8 ± 11.8	0.8590	66.6 ± 9.8	67.4 ± 11.4	0.9217

ABPM, ambulatory blood pressure monitoring; DBP, diastolic blood pressure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; SBP, systolic blood pressure.
Data shown as mean ± standard deviation.

during awake-time,[29] the development of the riser pattern seems to partly share a common mechanism in HFpEF and hypertension.

While therapeutic strategies with medical and non-medical treatments have been established in patients with HFrEF,[30–32] no effective therapies for HFpEF has been established. In patients with HFpEF, diuretics, ACEis, and ARBs are recommended to improve symptoms or reduce HF rehospitalization. Given that the riser pattern of SBP was associated with an increased risk of adverse outcomes among patients with HFpEF, the present study may provide a new treatment strategy to attempt to better control the circadian rhythm in patients with HFpEF.

Up to now, the association between HF and sleep-disordered breathing (SDB) has been reported. Although SDB is broadly classified into two types, obstructive sleep apnoea and central sleep apnoea (CSA), CSA is more often associated with HF.[33–36] In SDB, the repeated episodes of apnoea, hypoxia, re-oxygenation, and arousal throughout the night cause further sympathetic nervous system activation. In actually, the relationship between SDB and nocturnal hypertension has been reported. In our study, it is possible that SDB may affect the riser pattern, but the relationship is unknown because there is no record of respiratory frequency and SpO_2 during sleep. Moreover, it was reported that continuous positive airway pressure (CPAP) and phrenic nerve stimulation therapy improved BP or the symptoms of patients with HF with CSA,[30] but no one had used CPAP at the time of ABPM in our study.

Another interesting finding of our present study is that the clinical significance of the riser pattern in patients with HFmrEF is similar to those with HFrEF. The aetiology of HFmrEF is more closely associated with that of HFrEF than with that of HFpEF. For example, the rates of ischaemic and dilated cardiomyopathy were high, while the rate of hypertensive heart disease was low. Moreover, ~40% of patients with HFmrEF and 30% of those with HFrEF had a history of myocardial infarction, but only 18% of patients with HFpEF did. These similarities in aetiology and background between HFmrEF and HFrEF may have influenced the results in this study.

The event rate in this study was slightly higher compared with the recent meta-analysis.[37] Although the reason is unclear, it may be affect by lower administration rates of beta-blockers or higher rate of co-morbidities, such as hypertension and diabetes mellitus, and lower eGFR.

There are several limitations to this study. First, the analysis in this study was the low power because the sample size was small. In particular, in cardiovascular death, multiple analyses mean that the significance *P* about 0.03 could have been a chance finding. Therefore, a large-scale prospective study will be necessary to confirm hypothesis in this study. Second, ABPM was performed under medications that have antihypertensive effects, because safety considerations

Figure 3 Kaplan–Meier event-free survival curves for (A) all-cause death and (B) cardiovascular death in patients with HFpEF, (C) all-cause death and (D) cardiovascular death in patients with HFmrEF, and (E) all-cause death and (F) cardiovascular death in patients with HFrEF in the riser group (dotted line) compared with the non-riser group (solid line). HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

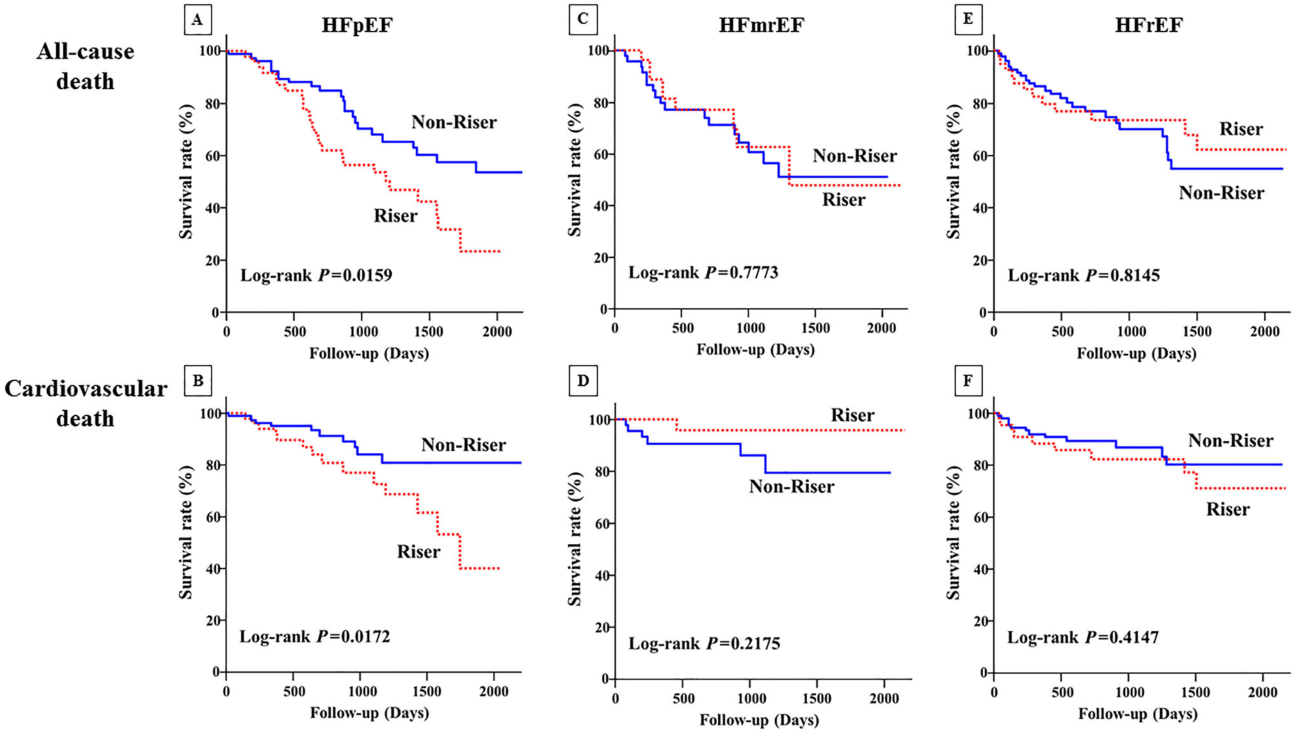


Table 4 Unadjusted and adjusted HRs for adverse outcomes in the riser and non-riser groups

	All-cause death			Cardiovascular death		
	Non-riser	Riser	*P* value	Non-riser	Riser	*P* value
HFpEF						
Unadjusted HR (95% CI)	1	1.97 (1.12–3.49)	0.0187	1	2.60 (1.16–6.06)	0.0206
Adjusted HR (95% CI)	1	2.01 (1.12–3.62)	0.0200	1	2.48 (1.08–5.90)	0.0332
HFmrEF						
Unadjusted HR (95% CI)	1	0.89 (0.38–1.96)	0.7763	1	0.28 (0.02–1.68)	0.1850
Adjusted HR (95% CI)	1	0.69 (0.28–1.64)	0.4044	1	0.21 (0.01–1.95)	0.2078
HFrEF						
Unadjusted HR (95% CI)	1	0.92 (0.45–1.80)	0.8137	1	1.43 (0.58–3.39)	0.4224
Adjusted HR (95% CI)	1	1.21 (0.57–2.45)	0.6048	1	2.16 (0.84–5.45)	0.1085

CI, confidence interval; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio.
Data shown as median (25th and 75th percentile). The Cox proportional hazards model adjusted for the following covariates: age, haemoglobin, estimated glomerular filtration rate, and B-type natriuretic peptide at discharge.

prevented halting their use. Therefore, it was not clear whether the circadian BP rhythm observed in this study was due to self-regulation, to the effect of the medications, or to both. Third, sleep-time was pre-determined based on the hospital hours and not individual patterns because we could not confirm accurate wake-up time and bedtime for each subject, which might alter the results of the circadian BP rhythm in ABPM, including nocturnal and riser patterns. Fourth, the subject included paroxysmal atrial fibrillation patients, and it is unknown whether or not it was atrial fibrillation rhythm during measurement.

In summary, the riser pattern is associated with an increased risk of adverse outcomes among patients with HFpEF but not in patients with HFrEF or HFmrEF. This finding may be related to the pathology of HFpEF and may help us to develop better treatment strategies.

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Conflict of interest

All authors declare no conflict of interest.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics of the HFpEF, HFmrEF, and HFrEF groups.
Table S2. Baseline characteristics in the HFpEF, HFmrEF, and HFrEF groups.

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