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The Association Between On-treatment Ambulatory Central Blood Pressure and Left Ventricular Reverse Remodeling in Heart Failure With Reduced Ejection Fraction

Jaehyung Ha, MD*, Chan Joo Lee, MD, PhD*, Jaewon Oh, MD, PhD, Sungha Park, MD, PhD, Sang-Hak Lee, MD, PhD, and Seok-Min Kang, MD, PhD

Division of Cardiology, Department of Internal Medicine, Severance Cardiovascular Hospital, Cardiovascular Research Institute, Yonsei University College of Medicine, Seoul, Korea

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Correspondence to
Seok-Min Kang, MD, PhD
Division of Cardiology, Department of Internal Medicine, Severance Cardiovascular Hospital, Cardiovascular Research Institute, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
Email: smkang@yuhs.ac

*Jaehyung Ha and Chan Joo Lee contributed equally to this work.

ABSTRACT

Background and Objectives: Compared to office blood pressure (OBP), central blood pressure (CBP) and ambulatory blood pressure (BP) are known to be better markers for predicting cardiovascular events. We evaluated the association between left ventricular reverse remodeling (LVRR) and ambulatory CBP in heart failure with reduced ejection fraction (HFrEF).
Methods: This study retrospectively analyzed 93 patients who performed ambulatory CBP and brachial BP (BBP) monitoring from 2018 to 2020 within 1 year after diagnosis of HFrEF at a single tertiary center. We analyzed the association between on-treatment ambulatory BPs and LVRR on follow-up echocardiography.
Results: The mean age of participants was 59 years; 65.6% were men; mean LVEF was 29%. Ambulatory BP and follow-up echocardiography were done at 143 days (interquartile range [IQR], 64–267) and 454 days (IQR, 281–600) after diagnosis of HF, respectively. Baseline OBP was not different between 2 groups, but ambulatory systolic CBP was significantly higher in the LVRR group than the non-LVRR group (p=0.005). Systolic OBP (odds ratio [OR], 1.029; confidence interval [CI], 1.004–1.055; p=0.026), 24-hour ambulatory systolic CBP (OR, 1.048; CI, 1.015–1.082; p=0.004), and 24-hour ambulatory systolic BBP (OR, 1.049; CI,1.017–1.082; p=0.003) were associated with LVRR. Compared to ambulatory systolic CBP of 110–119 mmHg, 90–99 mmHg showed lower OR for LVRR.
Conclusions: Low on-treatment ambulatory systolic CBP was closely related to a lower likelihood of LVRR in HFrEF than the normal range. Ambulatory CBP measured during treatment of patients with HFrEF appears to be useful in predicting outcomes.

Keywords: Blood pressure monitoring, ambulatory; Heart failure; Treatment outcome

INTRODUCTION

The incidence of heart failure (HF) is increasing worldwide as many countries' societies are rapidly aging.[1] In Korea, the incidence of HF is increasing gradually and the prevalence of HF was estimated at 2.24% in 2018.[2] Along with this trend in HF, numerous medications have

been studied to improve clinical outcomes, including cardiovascular death and readmission for HF. The cornerstone of medication for HF with reduced ejection fraction (HFrEF), including beta-blockers, renin-angiotensin system inhibitors, mineralocorticoid receptor antagonists (MRAs), angiotensin receptor neprilysin inhibitor (ARNI), and sodium-glucose cotransporter inhibitors, have been shown to have beneficial effects on cardiac remodeling.[3-5] This effect is referred to as left ventricular reverse remodeling (LVRR) and is characterized by a reduction in left ventricular (LV) chamber size and improvement in LV ejection fraction (LVEF).[6] LVRR has been known to be closely related to better clinical outcomes in HF,[3] and clinical predictors for LVRR have been described in many studies.[7] As a predictive marker for LVRR, office blood pressure (OBP) at baseline has been mentioned in some studies,[8-9] and a high OBP was found to be related to LVRR. Studies on on-treatment blood pressure (BP) in HF are relatively scarce, but it has shown that low on-treatment BP is related to poor outcomes.[10]

Meanwhile, ambulatory brachial BP (BBP) and central BP (CBP) have been proven to have greater predictive values than OBP in hypertensive patients.[11,12] CBP can be strongly related to clinical events because the major target organs are close to the aorta.[13] Regarding the relationship between CBP and HF, evidence of the association between CBP and LVRR in HF is relatively scarce. Therefore, we aimed to find out the association between ambulatory CBP and LVRR in patients with HFrEF.

METHODS

Study design and population

This study retrospectively analyzed patients who underwent ambulatory CBP measurement at a tertiary hospital within 1 year after diagnosis of HFrEF from 2018 to 2020 were enrolled (n=112). We measured ambulatory BBP and CBP after taking HF medication in the patients with HFrEF for safety evaluation as part of HF management. HFrEF was defined as LVEF ≤40% measured by conventional 2-dimensional transthoracic echocardiography with typical symptoms or signs of HF, which is according to European guidelines for HF.[14] Patients who were less than 18 years old and those who underwent cardiac synchronization therapy implantation or heart transplantation were excluded. Additionally, to evaluate LVRR, patients without echocardiographic data available after ambulatory BP monitoring (ABPM) were excluded. Most patients were managed with guideline-directed medical treatment, and 24-hour ABPM was performed after the diagnosis of HFrEF. Clinical data, such as laboratory findings and medication for HF, were reviewed when patients were diagnosed with HFrEF. When the follow-up echocardiography was performed, the information on patients' medication was also collected. Daily doses of medication for HF were calculated as a percentage of the target doses that were recommended by the guideline.[14] Patient records were anonymized before analysis, and informed consent from the subjects was waived. This study was approved by the Institutional Review Board (IRB) of Severance Hospital (No. 2021-4431-003).

BP measurements

ABPM was performed using an automated oscillometric device (Mobil-O graph).[15] BP was measured every 30 minutes during ABPM. Daytime and nighttime were divided according to the diaries of each patient, and average values of 24 hours, daytime, and nighttime BP were used in the study. Pulse waves were recorded from a conventional brachial cuff, and the corresponding CBP was derived using a generalized transfer function. To find the diurnal patterns of ambulatory BP, the differences between mean values of daytime BP and nighttime BP were used, and dipping patterns were classified into 4 different groups (extreme dipping, dipping, non-dipping, and rising).[16] Baseline OBP data at the time when patients were diagnosed with HF were collected. We also reviewed BP values from different measurements (OBP, ambulatory BBP, and ambulatory CBP) at the same time ABPM was performed, which was defined as on-treatment BP in our study.

Definition of LVRR

Baseline and follow-up echocardiography was performed using M-mode and Doppler analysis according to the current guidelines.[17] LVEF was estimated using the biplane method, and LV end-diastolic dimension was measured by M-mode tracing or 2D-guided linear measurement. LVRR was defined as a case in which all of the following conditions were satisfied: (1) ≥10% absolute improvement in LVEF, (2) follow-up LVEF >40%, and (3) decrease in LV end-diastolic dimension ≥10%.[6]

Statistical analysis

Continuous variables in our study were tested for normality using the Shapiro-Wilk normality test. Variables with normal distribution are presented as mean ± standard deviation, and non-normally distributed variables are presented as medians with interquartile range (IQR). Categorical variables are described as numbers and percentages. Overall comparison of variables was done according to LVRR. To compare continuous variables with normal distribution, Student's t-test was used, and the Wilcoxon rank-sum test was performed for continuous variables with non-normal distribution. Categorical variables were compared using the χ^2 test or Fisher's exact test. To find a predictive marker for LVRR, clinical variables were analyzed using univariate logis-

tic regression and multivariate analyses, which included the variables with p value <0.05 in univariate analyses, were performed. To evaluate the predictive value of BP measurements, multivariate receiver operating characteristic (ROC) curve analyses were also performed. In these analyses, BP values from different types of measurements and other clinical variables used in multivariate analyses for LVRR were included. The area under the curve (AUC) of each ROC curve was compared using the Delong test.[18] We categorized BP into 6 categories for ambulatory systolic CBP (<90, 90–99, 100–109, 110–119, 120–129, ≥130 mmHg, with 110–119 mmHg as the reference). The effect of each BP category on the LVRR was determined by comparison to the reference category. The statistical software R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for the analyses.

RESULTS

A flowchart of this study is shown in **Figure 1**. A total of 93 patients were finally included in this analysis. Follow-up echocardiography was done 454 days (IQR, 281–600) after diagnosis of HF. In detail, the median duration between the diagnosis of HF and the measurement of ambulatory BP was 143 days (IQR, 64–267) and follow-up echocardiography was performed at 284 days (IQR, 161–430) after ABPM was performed. LVRR was observed in 41 patients (44.1%). Echocardiographic data at baseline and follow-up period was described in **Supplementary Table 1**.

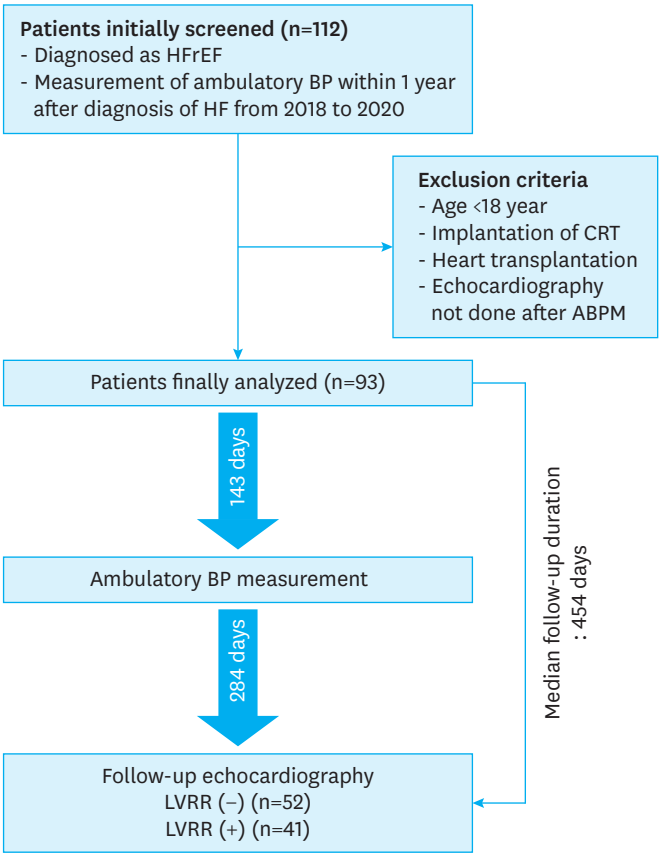

Figure 1. Flowsheet of the study.
ABPM = ambulatory blood pressure monitoring; BP = blood pressure; CRT = cardiac resynchronization therapy; HFrEF = heart failure with reduced ejection fraction; LVRR = left ventricular reverse remodeling.

Baseline characteristics and medications during follow-up

The demographic and clinical characteristics of the patients are summarized in **Table 1**. The mean age was 59 years; 65.6% of the patients were men. As for etiology of HF, 23% of the patients were diagnosed as ischemic HF. Main cause of non-ischemic HF was dilated cardiomyopathy (65.6% of all the patients) and about 12% of the patients were diagnosed with other diseases such as arrhythmogenic right ventricular cardiomyopathy, hypertrophic cardiomyopathy, and infiltrative heart disease. The median LVEF was 29%. Subjects were divided into the no LVRR (NLVRR) group (n=52) and the LVRR group (n=41). The LVRR group had a significantly lower EF than that of the NLVRR group (26% vs. 34%, p=0.002). Additionally, left bundle branch block (LBBB) was more prevalent (2.4% vs. 17.3%, p=0.02), and diastolic blood pressure (DBP) levels were significantly higher in the LVRR group than the NLVRR group (80 mmHg vs. 74 mmHg, p=0.011). Other clinical characteristics were not significantly different between the 2 groups.

At the time of ambulatory CBP measurements, beta-blockers were used in more than 95% of the patients, and they remained in use during the follow-up period. Renin-angiotensin system blocking agents, including angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, and ARNI, were also used in >90% of the study population during the study period. The MRA was used in all patients when ambulatory CBP was performed, but approximately only 74% of patients were treated with MRA when follow-up echocardiography was performed. At the when follow-up echocardiography was done, dose of ARNI was higher in LVRR group, but patterns of other medical therapy were not different between 2 groups (**Table 2**).

On-treatment BP according to LVRR

As shown in **Table 3**, the on-treatment systolic OBP in the LVRR group was significantly higher than that in the NLVRR group (p=0.041). The difference between the baseline and on-treatment systolic blood pressure (SBP) values were comparable between the 2 groups (NLVRR group: 121±19 mmHg to 113±19 mmHg [−8 mmHg] vs. LVRR group: 129±25 mmHg to 121±20 mmHg [−8 mmHg]; p=0.999). The 24-hour, daytime, and nighttime ambu-

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Table 1. Baseline characteristics according to LVRR

Characteristics	NLVRR (n=52)	LVRR (n=41)	Total (n=93)	p value
Age (year)	60±14	58±15	59±14	0.530
Male	33 (63.5)	28 (68.3)	61 (65.6)	0.789
BMI (kg/m^2)	23.9 (21.5–26.3)	23.5 (21.2–26.5)	23.7 (21.5–26.3)	0.816
SBP (mmHg)	121±19	129±25	124±22	0.080
DBP (mmHg)	72 (66–83)	80 (74–89)	76 (68–86)	0.011
LVEF (%)	34 (24–38)	26 (22–32)	29 (22–37)	0.002
LVEDD (mm)	62±10	63±7	62±7	0.590
Hemoglobin (g/dL)	13.2±2.0	13.9±2.3	13.5±2.2	0.117
BUN (mg/dL)	19.1 (15.4–25.0)	21.1 (15.7–24.3)	19.6 (15.5–24.8)	0.975
Cr (mg/dL)	1.0 (0.8–1.2)	1.0 (0.8–1.5)	1.0 (0.8–1.3)	0.414
Total cholesterol (mg/dL)	160 (136–188)	166 (148–187)	163 (139–187)	0.363
HDL-cholesterol (mg/dL)	42 (34–52)	42 (35–49)	42 (35–50)	0.985
LDL-cholesterol (mg/dL)	88 (63–108)	94 (73–132)	89 (68–118)	0.086
Triglyceride (mg/dL)	135 (94–191)	124 (105–161)	126 (96–190)	0.923
NT-proBNP (pg/mL)	661 (281–3,194)	2,014 (247–5,440)	969 (268–3,515)	0.585
Hypertension	21 (40.4)	17 (41.5)	38 (40.9)	0.999
Type 2 diabetes	12 (23.1)	8 (19.5)	20 (21.5)	0.872
Chronic kidney disease	10 (19.2)	9 (22.0)	19 (20.4)	0.949
Left bundle branch block	9 (17.3)	1 (2.4)	10 (10.8)	0.020
Atrial fibrillation	17 (32.7)	11 (26.8)	28 (30.1)	0.701
Etiology of heart failure				0.648
Ischemic heart failure	13 (25.0)	8 (19.5)	21 (22.6)	
DCMP	32 (61.5)	29 (70.7)	61 (65.6)	
Other disease	7 (13.5)	4 (9.8)	11 (11.8)	

Values are presented as mean ± standard deviation, number (%), or number (range).
LVRR = left ventricular reverse remodeling; NLVRR = no left ventricular reverse remodeling; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; LVEF = left ventricular ejection fraction; LVEDD = left ventricle end diastolic diameter; BUN = blood urea nitrogen; Cr = creatinine; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NT-proBNP = N-terminal pro-brain natriuretic peptide.

Table 2. Medications for heart failure during follow-up period according to LVRR

Target dose of medication	When ambulatory BP was done				When follow-up echocardiography was done			
	NLVRR (n=52)	LVRR (n=41)	Total (n=93)	p value	NLVRR (n=52)	LVRR (n=41)	Total (n=93)	p value
BB	50 (96.2)	40 (97.6)	90 (96.8)	0.999	51 (98.1)	40 (97.6)	91 (97.8)	0.999
≥25%	25 (48.1)	25 (61.0)	50 (53.8)	0.303	28 (53.8)	26 (63.4)	54 (58.1)	0.473
≥50%	5 (9.6)	11 (26.8)	16 (17.2)	0.057	13 (25.0)	11 (26.8)	24 (25.8)	0.999
ACEi/ARB	18 (34.6)	10 (24.4)	28 (30.1)	0.401	2 (3.8)	2 (4.9)	4 (4.3)	0.999
≥25%	9 (17.3)	8 (19.5)	17 (18.3)	0.998	2 (3.8)	2 (4.9)	4 (4.3)	0.999
≥50%	4 (7.7)	5 (12.2)	9 (9.7)	0.707	1 (1.9)	2 (4.9)	3 (3.2)	0.834
ARNI	31 (59.6)	30 (73.2)	61 (65.6)	0.252	44 (84.6)	37 (90.2)	81 (87.1)	0.622
≥25%	20 (38.5)	20 (48.8)	40 (43.0)	0.431	27 (51.9)	25 (61.0)	52 (55.9)	0.508
≥50%	10 (19.2)	14 (34.1)	24 (25.8)	0.163	17 (32.7)	24 (58.5)	41 (44.1)	0.022
MRA	52 (100.0)	41 (100.0)	93 (100.0)	0.999	38 (73.1)	31 (75.6)	69 (74.2)	0.969
≥25%	47 (90.4)	31 (75.6)	78 (83.9)	0.101	38 (73.1)	31 (75.6)	69 (74.2)	0.969
≥50%	21 (40.4)	13 (31.7)	34 (36.6)	0.518	19 (36.5)	14 (34.1)	33 (35.5)	0.983
Ivabradine	10 (19.2)	10 (24.4)	20 (21.5)	0.729	11 (21.2)	10 (24.4)	21 (22.6)	0.904
≥50%	7 (13.5)	8 (19.5)	15 (16.1)	0.614	7 (13.5)	8 (19.5)	15 (16.1)	0.614

LVRR = left ventricular reverse remodeling; BP = blood pressure; NLVRR = no left ventricular reverse remodeling; BB = beta-blocker; ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; MRA = mineralocorticoid receptor antagonist.

latory systolic CBP were higher in the LVRR group than in the NLVRR group (all p<0.01). However, the diastolic CBP levels did not differ between the 2 groups. Similarly, ambulatory systolic BBP levels were higher in the LVRR group than in the NLVRR group; however, ambulatory diastolic BBP levels were not different between the 2 groups.

The association between on-treatment SBPs and LVRR

To investigate the baseline clinical variables related to LVRR, logistic regression analysis was performed (**Supplementary Table 2**). In the univariate logistic regression models, DBP, LVEF, and LBBB were related to LVRR. These variables were included in multivariate logistic regression analysis to evaluate the association between

Table 3. On-treatment blood pressure according to LVRR

Type of BP	NLVRR (n=52)	LVRR (n=41)	Total (n=93)	p value
OBP (mmHg)				
Systolic OBP	113±19	121±20	116±20	0.041
Diastolic OBP	68±15	72±16	70±15	0.257
Ambulatory CBP (mmHg)				
24-hour systolic CBP	101±15	112±18	115±18	0.003
24-hour diastolic CBP	72±11	76±12	73±11	0.139
Daytime systolic CBP	103±15	114±18	117±18	0.002
Daytime diastolic CBP	75±11	78±13	75±11	0.143
Nighttime systolic CBP	98±16	109±19	112±19	0.005
Nighttime diastolic CBP	67 (61–73)	71 (63–79)	69 (61–77)	0.115
Ambulatory BBP (mmHg)				
24-hour systolic BBP	111±16	121±19	106±17	0.004
24-hour diastolic BBP	72±11	75±12	74±11	0.138
Daytime systolic BBP	113±15	124±19	108±17	0.002
Daytime diastolic BBP	73±11	77±12	76±12	0.148
Nighttime systolic BBP	107±17	117±20	103±18	0.007
Nighttime diastolic BBP	65 (59–72)	70 (63–77)	67 (61–75)	0.110

LVRR = left ventricular reverse remodeling; NLVRR = no left ventricular reverse remodeling; BBP = brachial blood pressure; CBP = central blood pressure; OBP = office blood pressure.

Table 4. ORs and 95% CIs per 1 mmHg increment of blood pressure for left ventricular reverse remodeling, adjusted for baseline characteristics

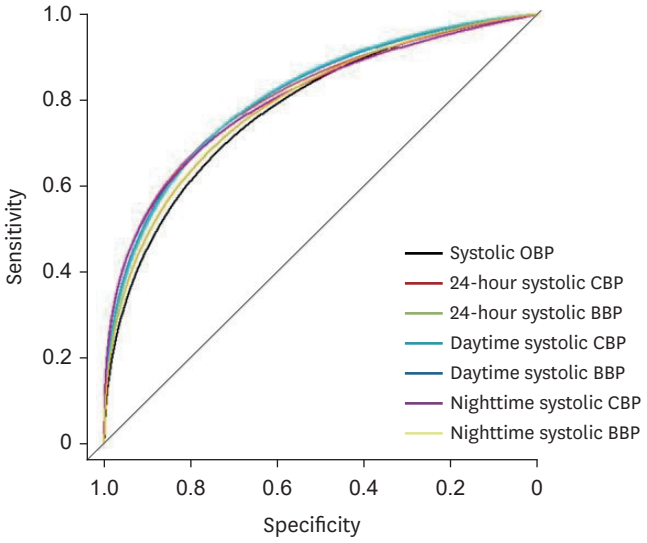
Type of BP	OR	95% CI	p value
OBP (mmHg)			
Systolic OBP	1.029	1.004–1.055	0.026
Diastolic OBP	1.013	0.982–1.044	0.420
Ambulatory CBP (mmHg)			
24-hour systolic CBP	1.048	1.015–1.082	0.004
24-hour diastolic CBP	1.029	0.988–1.072	0.162
Daytime systolic CBP	1.052	1.017–1.088	0.003
Daytime diastolic CBP	1.026	0.986–1.068	0.210
Nighttime systolic CBP	1.041	1.012–1.070	0.005
Nighttime diastolic CBP	1.033	0.994–1.073	0.098
Ambulatory BBP (mmHg)			
24-hour systolic BBP	1.049	1.017–1.082	0.003
24-hour diastolic BBP	1.029	0.987–1.072	0.175
Daytime systolic BBP	1.053	1.019–1.088	0.002
Daytime diastolic BBP	1.026	0.985–1.069	0.215
Nighttime systolic BBP	1.040	1.012–1.069	0.004
Nighttime diastolic BBP	1.034	0.994–1.076	0.096

Each model was adjusted for baseline office diastolic blood pressure, left ventricular ejection fraction, and left bundle branch block.
OR = odds ratio; CI = confidence interval; BBP = brachial blood pressure; CBP = central blood pressure; OBP = office blood pressure.

on-treatment SBP and LVRR. Multivariable models adjusted for baseline DBP, LVEF, and LBBB showed that high on-treatment systolic OBP (OR, 1.029; confidence interval [CI], 1.004–1.055; p=0.026), 24-hour ambulatory systolic CBP (OR, 1.048; CI, 1.015–1.082; p=0.004), and 24-hour ambulatory systolic BBP (OR, 1.049; CI,1.017–1.082; p=0.003) were significantly associated with LVRR (**Table 4**). On-treatment DBP levels were not related to LVRR. Similarly, higher on-treatment daytime CBP (OR, 1.052; CI, 1.017–1.088; p=0.004), BBP (OR, 1.053; CI, 1.019–1.088; p=0.002) and nighttime CBP (OR, 1.041; CI, 1.012–1.070; p=0.003), BBP (OR, 1.040; CI, 1.012–1.069; p=0.004) were related to better LVRR.

Predictive value of OBP, ambulatory BBP and ambulatory CBP for LVRR

To evaluate the predictive value for LVRR of in the different types of BP measurements, ROC curves were drawn, and the AUCs for each curve were calculated (**Figure 2**). Since the levels of on-treatment DBP did not show a significant relationship with LVRR, only the values of SBP from different BP measurements were used to draw ROC curves. When the AUCs of each BP measurement were compared, the AUCs of systolic OBP (0.780; 95% CI, 0.685–0.874), ambulatory 24-hour systolic CBP (0.802; 95% CI, 0.710–0.892), and ambulatory 24-hour systolic BBP (0.801; 95% CI, 0.711–0.891) were not significantly different (all p>0.05). The AUCs of daytime and nighttime ambulatory BP showed similar results.



AUC of each BP measurement (95% CI)	
Systolic OBP	0.780 (0.685–0.874)
24-hour systolic CBP	0.802 (0.710–0.892)
24-hour systolic BBP	0.801 (0.711–0.891)
Daytime systolic CBP	0.801 (0.710–0.891)
Daytime systolic BBP	0.804 (0.716–0.893)
Nighttime systolic CBP	0.803 (0.712–0.900)
Nighttime systolic BBP	0.794 (0.703–0.885)

Figure 2. Receiver operating characteristic curve for prediction of left ventricular reverse remodeling according to each BP measurement.
AUC = area under the curve; BBP = brachial blood pressure; BP = blood pressure; CI = confidence interval; CBP = central blood pressure; OBP = office blood pressure.

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Table 5. Adjusted ORs for LVRR according to on-treatment 24-hour systolic CBP

24-hour systolic CBP (mmHg)	Number of patients with LVRR (%)	Adjusted OR (95% CI)	p value
<90	7 of 18 (38.9)	0.469 (0.096–2.288)	0.349
90–99	3 of 17 (17.7)	0.101 (0.016–0.656)	0.016
100–109	8 of 21 (38.1)	0.304 (0.064–1.445)	0.134
110–119	9 of 16 (56.3)	1.000 (reference)	
120–129	5 of 11 (45.4)	0.762 (0.119–4.869)	0.774
≥130	9 of 10 (90.0)	4.376 (0.403–47.505)	0.225

ORs were adjusted for baseline office diastolic blood pressure, left ventricular ejection fraction, and left bundle branch block.
OR = odds ratio; CI = confidence interval; CBP = central blood pressure; LVRR = left ventricular reverse remodeling.

Optimal BP range of ambulatory CBP related to LVRR

Compared to the reference BP range, 90–99 mmHg of ambulatory systolic CBP showed a significantly lower odds ratio (OR) for the LVRR (**Table 5**). BP ranges below the reference range tended to have lower ORs, and the range of ≥130 mmHg had a higher OR for LVRR, but these were not statistically significant. Similarly, the result of ambulatory 24-hour systolic BBP showed a tendency that lower BP ranges had lower ORs and ≥130 mmHg had higher OR than the reference range (**Supplementary Table 3**).

Dipping patterns of ambulatory BP according to LVRR

With ambulatory SBP data, dipping patterns were analyzed (**Table 6**). The dominant dipping pattern of the patients was non-dipping pattern (systolic CBP: 48.4%, systolic BBP: 52.7%). Proportions of non-dipping pattern of systolic CBP were higher in the LVRR group than the NLVRR group (55.8% vs. 39.0%), but overall patterns were not different between the 2 groups (p=0.807). The dipping pattern of systolic BBP was not different from that of systolic CBP, so there was no significant difference between the 2 groups. Additionally, occurrence of LVRR in the patients with non-dipping pattern was not different compared to the others (OR. 1.379; 95% CI. 0.543–3.503; p=0.499).

Table 6. Dipping pattern of on-treatment systolic blood pressure according to LVRR

Dipping pattern	NLVRR (n=52)	LVRR (n=41)	Total (n=93)	p value
Systolic CBP				
Daytime–Nighttime				0.723
≥20 mmHg	2 (3.8)	3 (7.3)	5 (5.4)	
≥10 mmHg but <20 mmHg	11 (21.2)	10 (24.4)	21 (22.6)	
≥0 mmHg but <10 mmHg	27 (51.9)	16 (39.0)	43 (46.2)	
≥−10 mmHg but <0 mmHg	11 (21.2)	10 (24.4)	21 (22.6)	
≥−20 mmHg but <−10 mmHg	1 (1.9)	1 (2.4)	2 (2.2)	
<−20 mmHg	0 (0.0)	1 (2.4)	1 (1.1)	
(Daytime–Nighttime)/Daytime				0.807
≥20% (extreme dipping)	1 (1.9)	1 (2.4)	2 (2.2)	
≥10% but <20% (dipping)	10 (19.2)	12 (29.3)	22 (23.7)	
≥0% but <10% (non dipping)	29 (55.8)	16 (39.0)	45 (48.4)	
<0% (rising)	12 (23.1)	12 (29.3)	24 (25.8)	
Systolic BBP				
Daytime–Nighttime				0.215
≥20 mmHg	1 (1.9)	4 (9.8)	5 (5.4)	
≥10 mmHg but <20 mmHg	13 (25.0)	12 (29.3)	25 (26.9)	
≥0 mmHg but <10 mmHg	28 (53.8)	15 (36.6)	43 (46.2)	
≥−10 mmHg but <0 mmHg	9 (17.3)	7 (17.1)	16 (17.2)	
≥−20 mmHg but <−10 mmHg	1 (1.9)	3 (7.3)	4 (4.3)	
<−20 mmHg	0 (0.0)	0 (0.0)	0 (0.0)	
(Daytime–Nighttime)/Daytime				0.523
≥20% (extreme dipping)	1 (1.9)	0 (0.0)	1 (1.1)	
≥10% but <20% (dipping)	11 (21.2)	12 (29.3)	23 (24.7)	
≥0% but <10% (non dipping)	30 (57.7)	19 (46.3)	49 (52.7)	
<0% (rising)	10 (19.2)	10 (24.4)	20 (21.5)	

LVRR = left ventricular reverse remodeling; NLVRR = no left ventricular reverse remodeling; BBP = brachial blood pressure; CBP = central blood pressure.

DISCUSSION

In our study, we found that the on-treatment systolic CBP was higher in the LVRR group than in the NLVRR group. Furthermore, higher on-treatment systolic CBP was significantly associated with more LVRR even after adjustment for baseline clinical characteristics. Compared to the normal range of ambulatory CBP, lower ranges showed the tendency of a lower likelihood of LVRR. However, as to predictive value for LVRR, there was no significant difference among OBP, ambulatory BBP, and ambulatory CBP. With these results, our study may be meaningful because it is the first to evaluate the prognostic value of on-treatment ambulatory CBP in patients with HFrEF.

Major organs, including the heart, are directly exposed to aortic pressure and not brachial pressure. CBP, which measures the pressure of the aorta, can be a strong predictive marker for cardiovascular events and it have been shown that the superiority of CBP as a prognostic factor compared to BBP in non-HF patients.[12] In addition, it has been demonstrated that 24-hour ambulatory BP is more correlated with target organ damage and has better prognostic significance than OBP.[19] As ambulatory CBP, 24-hour ambulatory systolic CBP showed a tendency to be more closely related to LV mass and LV hypertrophy than 24-hour ambulatory systolic BBP and systolic OBP.[20] Based on this background, we expected that ambulatory CBP would be also a good prognostic marker in patients with HF. Recovery of LV function by medical or device treatment in patients with HFrEF is called LVRR and is associated with less HF hospitalization and reduction of cardiovascular mortality.[3] Therefore, we set LVRR as a surrogate marker for prognosis in HFrEF patients in this study.

By calculating the AUCs of each ROC curve from different types of BP measurements, we attempted to find out the prognostic power of ambulatory systolic CBP for LVRR. Since the main in-

terest of this study was CBP measured in the ambulatory setting, it was expected that it would be a superior marker than OBP or ambulatory BBP in also HF patients. However, there was no statistically significant difference in AUC among systolic OBP, 24-hour ambulatory systolic CBP, and 24-hour ambulatory systolic BBP. While these results were outside of our expectations, they are not very different from previous studies. In the study by Sung et al.[21] which showed the association between SBP (including CBP and BBP) and 6-month cardiovascular events, the hazard ratios of systolic BBP and systolic CBP were 1.48 and 1.49, respectively, which were almost the same. A prospective longitudinal study from the Chronic Renal Insufficiency Cohort showed that both the highest quartile of systolic CBP and the highest quartile of systolic BBP were associated with an increased risk of composite cardiovascular outcomes with similar hazard ratios.[22] As shown in these studies, because systolic BBP and CBP are highly correlated with each other, the statistical power to determine which of the 2 BP measurements is superior may have been insufficient. A further prospective study with a larger number of patients is needed to clarify the predictive value of CBP in the patient with HFrEF.

Hypertension is known to be the main etiology of HF and lowering BP with antihypertensive drugs has reduced the risk for HF development.[23] However, several studies of patients with HF found that lower BP was related to worse prognoses,[24,25] and there is no consensus regarding the optimal target of BP in especially HFrEF. A study from the Korean HF registry showed a reverse J-curve relationship between the on-treatment systolic OBP and clinical events. In this study, systolic OBP of 132 mmHg was associated with the lowest risk of all-cause mortality. Systolic OBP <132 mmHg was associated with a tendency of higher risk than the other group; however, the association between systolic OBP more than 132 mmHg and mortality risk was indefinite.[10] According to the analysis results of the OPTIMIZE-HF registry, SBP <130 mmHg at discharge is associated with poor outcomes among patients hospitalized with HFrEF.[26] In our study, the on-treatment 24-hour systolic CBP of 90–99 mmHg showed a lower likelihood of LVRR than 110–119 mmHg (**Table 5**). In terms of ambulatory systolic BBP (**Supplementary Table 3**), the results were like those of CBP. Our results indicate that LVRR occurs less frequently at a low BP, which is like the results of previous studies on the optimal BP range in HFrEF. On contrary to results of ambulatory systolic CBP and BBP, the analysis of OBP ranges did not show a significant association with LVRR (**Supplementary Table 4**), which may provide some clues about the superiority of ambulatory BP as a predictive marker for HF over OBP.

We found the positive relationship between on-treatment SBP and LVRR, but this result should be interpretated carefully. Lower on-treatment SBP might reflect poorer LV systolic function. Patients who showed LVRR might have improved LVEF more than the other groups, which might have led to higher on-treatment SBP. BP is determined by the interaction between LV systolic function, arterial stiffness, and vascular resistance. In particular, SBP is affected by LV stroke volume.[27] Therefore, an increase in SBP during treatment in patients with HFrEF may be a marker of an improvement in LV systolic function caused by LVRR. Similarly, one study showed that BBP and CBP increased in patients with a clinical response after cardiac resynchronization therapy, but there was no increase in non-responder patients.[28] To find out the relationship between LVEF and on-treatment SBP, we further analyzed the association between follow-up LVEF and on-treatment SBP and there was a significant interaction (data not shown). In other words, higher LVEF was related to higher on-treatment SBP. However, even after adjusting for follow-up LVEF, the on-treatment ambulatory systolic CBP and systolic BBP were significantly associated with LVRR (data not shown). On the other hand, patients with a higher on-treatment BP were prescribed medication more intensively. Comparing the doses of medications according to on-treatment BP, we found that beta blockers and ARNI with higher dose were used in patients with higher BP (**Supplementary Table 5**). Also, higher dose of ARNI at the follow-up period was prescribed in LVRR group (**Table 2**).

With the results of higher occurrence of LVRR in the patients with higher on-treatment systolic CBP, it should not be interpreted to mean that higher BP should be maintained in management of HF. In the subjects of our study, guideline-directed medical therapy was titrated to the optimal dose according to the clinical situation. Although randomized clinical trials for target BP in HF were limited, target BP of HF is not different from other cardiovascular diseases in current guidelines of hypertension.[29]

Our study has some limitations. This study was retrospective and from a single center. We only evaluated patients who were monitored by ABPM; hence, selection bias might have occurred, and the results of our study could be difficult to apply to all HF patients. In addition, a relatively small number of patients were enrolled; therefore, a larger study for on-treatment CBP is warranted. Furthermore, we used multivariate analysis with limited variables; therefore, other confounding factors not included in the model could have affected the analysis. Also, the healthier patients with higher BP could tolerate higher dose of medication, which might lead to more LVRR. However, despite these causable factors, we focused on the "on-treatment BP," and this study may be meaningful since the clinical implication of the study was to find out the relationship between on-treatment ambulatory CBP and LVRR.

In our study, LVRR was used as an indicator of HF prognosis. We did not evaluate clinical events because the number of study population was small, and the follow-up duration was relatively short. A long-term follow-up study with a larger number of patients that evaluates the association between on-treatment ambulatory CBP and clinical events will clearly reveal the role of on-treatment ambulatory CBP as a predictive marker.

We found that the higher on-treatment ambulatory systolic CBP was associated with more LVRR in patients with HFrEF. Low on-treatment ambulatory systolic CBP was closely related to a lower likelihood of LVRR in HFrEF than the normal range. The predictive power of systolic CBP was not significantly different from other BP measurements. In addition, dipping patterns of on-treatment systolic CBP were not associated with LVRR. Although limited, this study provides evidence that ambulatory systolic CBP may help predict prognosis in patients with HFrEF.

ORCID iDs
Jaehyung Ha
https://orcid.org/0000-0001-7049-5422
Chan Joo Lee
https://orcid.org/0000-0001-5362-478X
Jaewon Oh
https://orcid.org/0000-0002-4585-1488
Sungha Park
https://orcid.org/0000-0001-5362-478X
Sang-Hak Lee
https://orcid.org/0000-0002-4535-3745
Seok-Min Kang
https://orcid.org/0000-0001-9856-9227

Conflict of Interest
The authors have no financial conflicts of interest.

Author Contributions
Conceptualization: Ha J, Lee CJ, Oh J, Park S, Lee SH, Kang SM; Data curation: Ha J, Lee CJ; Formal analysis: Ha J, Lee CJ; Funding acquisition: Ha J, Lee CJ; Investigation: Ha J, Lee CJ, Oh J, Kang SM; Methodology: Ha J, Lee CJ, Oh J, Kang SM; Project administration: Ha J, Lee CJ, Kang SM; Resources: Ha J, Lee CJ; Software: Ha J, Lee CJ; Supervision: Ha J, Lee CJ; Validation: Ha J, Lee CJ; Visualization: Ha J, Lee CJ; Writing - original draft: Ha J, Lee CJ; Writing - review & editing: Ha J, Lee CJ, Oh J, Park S, Lee SH, Kang SM.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Echocardiographic parameters at baseline and follow-up

Click here to view

Supplementary Table 2
Baseline characteristics related to left ventricular reverse remodeling

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Supplementary Table 3
Adjusted ORs for LVRR according to on-treatment 24-hour systolic BBP

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Supplementary Table 4
Adjusted ORs for LVRR according to on-treatment systolic OBP

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Supplementary Table 5
Medication for heart failure according to median value of on-treatment ambulatory 24-hour systolic central blood pressure

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