Received: 19 October 2020 | Revised: 2 January 2021 | Accepted: 21 January 2021

DOI: 10.1111/jch.14204

SHORT REPORT

WILEY

Quantitative evaluation of white matter hyperintensities in patients with heart failure using an innovative magnetic resonance image analysis method: Association with disrupted circadian blood pressure variation

Takahiro Komori MD, PhD[1] | Satoshi Hoshide MD, PhD[1] | Ken-ichi Tabei MD, PhD[2] | Hidekazu Tomimoto MD, PhD[2] | Kazuomi Kario MD, PhD[1]

[1]Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Tochigi, Japan

[2]Department of Neurology, Graduate School of Medicine, Mie University, Mie, Japan

Correspondence
Kazuomi Kario, Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, 3311-1, Yakushiji, Shimotsuke, Tochigi 329-0498, Japan.
Email: kkario@jichi.ac.jp

Funding information
Japan Society for the Promotion of Science, Grant/Award Number: 16K19318

Abstract

White matter hyperintensities (WMHs) are risk factors for future cognitive impairment and are associated with an abnormal circadian blood pressure (BP) rhythm in patients with hypertension. However, whether this association exists in patients with heart failure (HF) is unclear. We performed a cross-sectional study of hospitalized patients with HF who underwent ambulatory BP monitoring and brain magnetic resonance imaging (MRI). A non-dipper BP pattern was defined as a < 10% nocturnal BP decline. WMHs on brain MRI scans were quantitated using a novel image analysis software (FUSION: FUsed Software for Imaging Of Nervous system). We enrolled 28 hospitalized patients with HF (age: 70.0 ± 9.8 years, 64.3% men). In the brain MRI analysis, the non-dipper group had higher WMH volume (18.9 ± 19.8 vs. 7.7 ± 8.3 mL, $P = .047$) and percentage of WMH/total brain volume (1.31 ± 1.28% vs. 0.55 ± 0.58%, $P = .04$) than the dipper group. In conclusion, using the newly developed MRI analysis software, we successfully quantitatively measured the volume of WMHs and found that the WMH volume increased 2.4 times in patients with a non-dipper pattern of nocturnal BP compared with those with a normal dipper pattern.

1 | INTRODUCTION

White matter hyperintensity (WMH) is a chronic ischemic change of the brain, and a risk factor for future stroke and cognitive impairment (CI). Although blood pressure (BP) elevation is an important risk factor for WMHs, increased nocturnal BP is especially associated with the incidence of WMHs in the brain of patients with hypertension.[1]

The number of elderly patients with heart failure (HF) has been increasing worldwide. Physical frailty and neurocognitive frailty are frequently observed in elderly patients with HF. We previously reported that CI is associated with nocturnal BP elevation in patients with HF.[2] Therefore, we hypothesized that increased nocturnal BP may be associated with the incidence of WMHs in patients with HF, as there has been no study on this issue. We conducted the present study to investigate the association between nocturnal BP and WMH volume evaluated using an innovative quantitative analysis method.

2 | METHODS

This was a cross-sectional study of hospitalized patients with HF from July 2017 to March 2019. In this study, we enrolled the

patients who were diagnosed with HF in accordance with the current guideline for HF management by cardiologist[3] and agreed to perform ambulatory BP monitoring and brain magnetic resonance imaging (MRI) before discharge. All examinations were performed when the patients' symptoms improved. The study protocol was approved by the Institutional Review Board of Jichi Medical University School of Medicine. Informed consent was obtained from all patients.

When a patient's HF symptoms improved, non-invasive ambulatory BP monitoring was performed using an automatic system with electric cuff inflation (TM-2430; A&D), which recorded both BP (through the oscillometric method) and pulse rate every 30 min for 24 h. Sleep BP was defined as the average of BP measurements during the time the patients were in bed, and awake BP was defined as the average BP measurement recorded during the rest of the day. The nocturnal BP decline (%) was calculated as (awake SBP − sleep SBP)/awake SBP. We classified the patients' nocturnal BP decline as follows: non-dipper if it was <10% and dipper if it was ≥10%. Casual BP reading was taken twice after the patients rested for 5 min while seated, and the average of the two BP readings was used.

The patients enrolled in this study underwent brain magnetic resonance imaging (MRI) using MAGNETOM Skyra (Siemens; for the fluid-attenuated inversion recovery [FLAIR] images: repetition time [TR], 12,000 ms; echo time [TE], 125 ms; flip angle, 120; matrix size, 320 × 224; slice thickness, 5 mm; for the T2 images: TR, 6000 ms; TE, 98 ms; flip angle, 150; matrix size, 448 × 380; slice thickness, 5 mm), MAGNETOM Avanto (Siemens, Erlangen, Germany; for the FLAIR images: TR, 10,000 ms; TE, 104 ms; flip angle, 160; matrix size, 256 × 230; slice thickness, 5 mm; for the T2 images: TR, 6000 ms; TE, 89 ms; flip angle, 160; matrix size, 320 × 288; slice thickness, 5 mm), MAGNETOM Symphony (Siemens, Erlangen, Germany; for the FLAIR images: TR, 10,000 ms; TE, 109 ms; flip angle, 160; matrix size, 256 × 230; slice thickness, 5 mm; for the T2 images: TR, 6000 ms; TE, 93 ms; flip angle, 160; matrix size, 320 × 288; slice thickness, 5 mm), or Achieva (Philips, Eindhoven, Netherlands; for the FLAIR images: TR, 11,000 ms; TE, 140 ms; flip angle, 90; matrix size, 256 × 256; slice thickness, 5 mm; for the T2 images: TR, 6000 ms; TE, 200 ms; flip angle, 90; matrix size, 304 × 304; slice thickness, 5 mm).

FUSION (Fused Software for Imaging of Nervous system) software was used to calculate the total volume of WMHs and the total brain volume.[4] This software could analyze images taken using 3-T or 1.5-T MRI. The volume of WMHs, which appeared as hyperintense areas on FLAIR images, was quantified (Figure 1). To analyze the differences in WMH volume, the WMH volume was divided by the total brain volume and multiplied by 100 to yield a WMH percentage.

Data are expressed as mean ± standard deviation or percentages, or as median (interquartile range) for continuous variables or

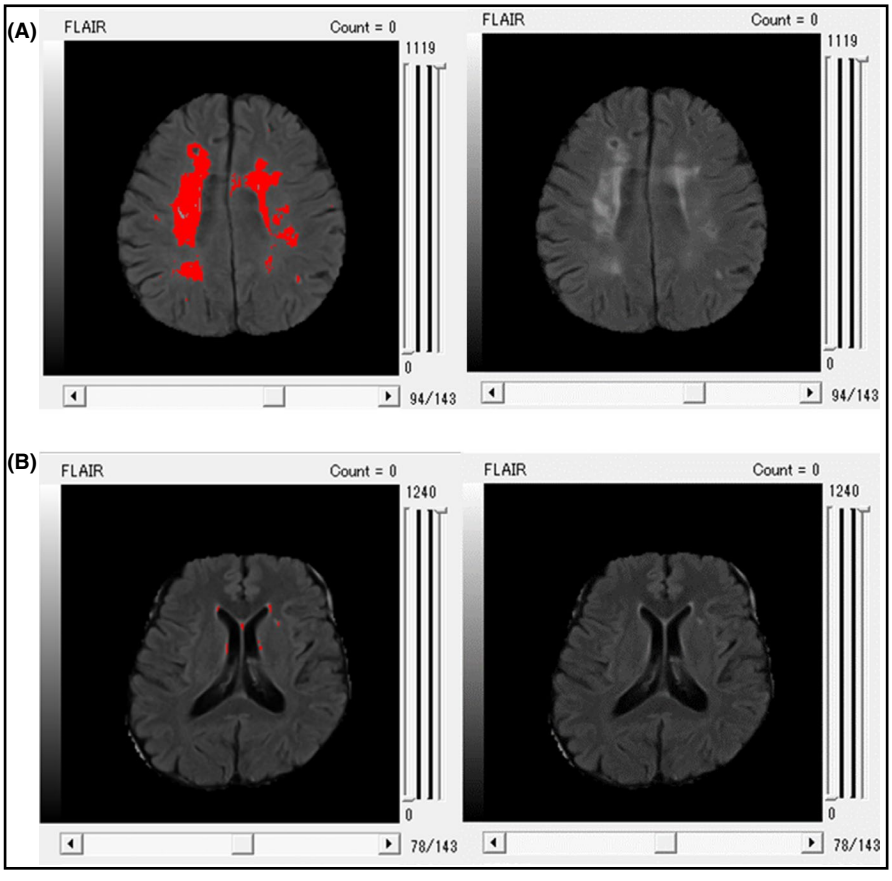

FIGURE 1 Quantitative evaluation of white matter hyperintensity. (A) Brain imaging scan of a patient with a non-dipper blood pressure pattern. A large amount of WMHs was detected (left image). Image before software analysis (right image). (B) Brain imaging scan of a patient with a dipper pattern. The amount of WMHs was small (left image). Image before software analysis (right image)

counts (percentages) for categorical variables. The unpaired t test was performed to test the mean differences between the non-dipper and dipper groups. The chi-square test was used to compare proportions. All statistical analyses were performed using SPSS version 26.0 (IBM).

3 | RESULTS

We enrolled 28 hospitalized patients with HF. When the patients were divided into the non-dipper and dipper groups according to nocturnal BP decline, sleep diastolic BP was significantly higher in the non-dipper

TABLE 1 Baseline characteristics

Variables	Non-dipper (*N* = 18)	Dipper (*N* = 10)	*P*-value
Age, years	70 ± 9	69 ± 11	0.76
Male sex, *n* (%)	10 (55.6)	8 (80.0)	0.19
Body mass index, kg/m^2	21.4 ± 4.7	22.8 ± 3.4	0.43
IHD, *n* (%)	5 (27.8)	5 (50.0)	0.22
Non-IHD, *n* (%)	13 (72.2)	5 (50.0)	0.22
HFpEF, *n* (%)	7 (38.9)	5 (50.0)	0.70
History of hypertension, *n* (%)	12 (66.7)	7 (77.8)	0.45
Diabetes, *n* (%)	5 (27.8)	4 (44.4)	0.33
Atrial fibrillation, *n* (%)	10 (55.6)	4 (40.0)	0.35
Cardiovascular drugs			
ACE inhibitor, *n* (%)	7 (41.2)	5 (50.0)	0.48
ARB, *n* (%)	8 (47.1)	4 (40.0)	0.52
β-blocker, *n* (%)	16 (94.1)	10 (100)	0.63
Diuretics, *n* (%)	15 (88.2)	7 (70.0)	0.25
Laboratory and physiological examinations			
Creatinine, mmol/L	1.3 ± 0.4	1.5 ± 0.6	0.35
Hemoglobin, g/dL	15.8 ± 8.0	13.4 ± 2.2	0.36
NT-proBNP, pg/mL	1340 (1074, 2360)	891 (495, 1227)	0.35
LVEF, %	48.0 ± 15.7	50.8 ± 15.7	0.66
Blood pressure and pulse rate			
Casual SBP, mm Hg	114 ± 19	115 ± 17	0.92
Casual DBP, mm Hg	67 ± 14	69 ± 16	0.83
Casual PR, bpm	66 ± 14	69 ± 8	0.59
24-h SBP, mm Hg	114 ± 18	111 ± 16	0.63
24-h DBP, mm Hg	72 ± 10	69 ± 7	0.52
24-h PR, bpm	63 ± 9	68 ± 6	0.22
Awake SBP, mm Hg	114 ± 17	116 ± 16	0.71
Awake DBP, mm Hg	73 ± 12	73 ± 7	0.98
Awake PR, bpm	64 ± 9	68 ± 7	0.34
Sleep SBP, mm Hg	114 ± 20	99 ± 15	0.06
Sleep DBP, mm Hg	71 ± 11	63 ± 7	0.048
Sleep PR, bpm	62 ± 11	67 ± 6	0.19
Brain MRI			
White matter volume, mL	434 ± 68	430 ± 65	0.90
Gray matter volume, mL	441 ± 99	448 ± 27	0.77
Total brain volume, mL	1371 ± 138	1386 ± 84	0.73
WMH volume, mL	18.9 ± 19.8	7.7 ± 8.3	0.047
WMH/total brain volume, %	1.31 ± 1.28	0.55 ± 0.58	0.04

Note: Abbreviations: DBP, diastolic blood pressure; HFpEF, heart failure with preserved ejection fraction; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-brain natriuretic peptide; PR, pulse rate; SBP, systolic blood pressure; WMH, white matter hyperintensity.

group than in the dipper group. The other baseline characteristics were similar between the two groups. In the brain MRI analysis, the non-dipper group showed higher WMH volume (18.9 ± 19.8 vs. 7.7 ± 8.3 mL, $P = .047$) and percentage of WMH/total brain volume (1.31 ± 1.28% vs. 0.55 ± 0.58%, $P = .04$) than the dipper group (Table 1).

4 | DISCUSSION

This is the first study to show, using an innovative quantitative image analysis software, that an abnormal circadian BP rhythm is associated with WMHs in patients with HF and those with hypertension.

The association between the non-dipper pattern and WMHs has been reported in hypertensive patients. However, this association has not been previously observed in patients with HF. WMHs are caused by ischemic brain damage, which may be augmented by hypoxia in patients with HF. Lung congestion and sleep apnea syndrome occur as complications in patients with HF and may lead to nocturnal hypoxia, which could result in the progression of WMHs. In addition, the cause of a non-dipper pattern has been considered to be fluid retention, sleep apnea syndrome, and sympathetic nervous system activation, which are comorbid conditions in HF.

Previous studies have reported that the severity of WMHs is associated with CI in hypertensive patients.[5] However, the clinical significance of WMHs in patients with HF has not been established. A few studies have investigated the association between CI and brain imaging findings in patients with HF. A previous report has shown that temporal lobe atrophy, not WMHs and global brain atrophy, is related to CI in patients with HF.[6] WMHs have been associated with depression and anxiety in patients with HF.[7] There are several limitations in the present study. Whether our findings are specific in the patients with HF has been remained. Future study is needed to investigate the difference in our findings between the patients with and without HF. Another important limitation was that the number of patients was small. Our findings need to be confirmed in the study included a large number of patients.

5 | CONCLUSIONS

Using an innovative MRI analysis software, we successfully quantitatively measured the volume of WMHs and found that the WMH volume increased 2.4 times in patients with a non-dipper pattern of nocturnal BP compared with those with a normal dipper pattern.

ACKNOWLEDGMENTS

This work was supported by Japan Society for the Promotion of Science KAKENHI grant no. 16K19318.

CONFLICT OF INTEREST

All authors report no potential conflicts of interest in relation to this article.

AUTHOR CONTRIBUTIONS

T. Komori collected and analyzed the data and wrote the Introduction, Methods, Results, and Discussion sections. S. Hoshide, H. Tomimoto and K. Kario reviewed/edited the manuscript. K. Tabei and H. Tomimoto contributed to develop the image analysis software. K. Kario supervised the conduct of the study and data analysis.

ORCID

Takahiro Komori https://orcid.org/0000-0003-2591-0433
Satoshi Hoshide https://orcid.org/0000-0001-7541-5751
Kazuomi Kario https://orcid.org/0000-0002-8251-4480

REFERENCES

1. Kokubo M, Shimizu A, Mitsui T, et al. Impact of night-time blood pressure on cerebral white matter hyperintensity in elderly hypertensive patients. *Geriatr Gerontol Int*. 2015;15(Suppl 1):59-65.
2. Komori T, Eguchi K, Saito T, Nishimura Y, Hoshide S, Kario K. Riser blood pressure pattern is associated with mild cognitive impairment in heart failure patients. *Am J Hypertens*. 2016;29:194-201.
3. Tsutsui H, Isobe M, Ito H, et al. Jcs 2017/jhfs 2017 guideline on diagnosis and treatment of acute and chronic heart failure— digest version. *Cic J*. 2017;2019(83):2084-2184.
4. Tabei KI, Kida H, Hosoya T, Satoh M, Tomimoto H. Prediction of cognitive decline from white matter hyperintensity and single-photon emission computed tomography in alzheimer's disease. *Front Neurol*. 2017;8:408.
5. Smith EE, Egorova S, Blacker D, et al. Magnetic resonance imaging white matter hyperintensities and brain volume in the prediction of mild cognitive impairment and dementia. *Arch Neurol*. 2008;65:94-100.
6. Frey A, Sell R, Homola GA, et al. Cognitive deficits and related brain lesions in patients with chronic heart failure. *JACC Heart Fail*. 2018;6:583-592.
7. Vogels RL, Oosterman JM, van Harten B, et al. Neuroimaging and correlates of cognitive function among patients with heart failure. *Dement Geriatr Cogn Disord*. 2007;24:418-423.

How to cite this article: Komori T, Hoshide S, Tabei K-I, Tomimoto H, Kario K. Quantitative evaluation of white matter hyperintensities in patients with heart failure using an innovative magnetic resonance image analysis method: Association with disrupted circadian blood pressure variation. *J Clin Hypertens*. 2021;23:1089–1092. https://doi.org/10.1111/jch.14204