Nocturnal blood pressure and left ventricular hypertrophy in patients with diabetes mellitus

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Funding Sources:

YH is supported by research grants from the Vehicle Racing Commemorative Foundation, the Takeda Science Foundation and the Mitsui Sumitomo Insurance Welfare Foundation, and a JSPS KAKENHI grant (Number JP23K07501). MS is supported by a research grant from the Vehicle Racing Commemorative Foundation, a JSPS KAKENHI grant (Number JP22H03069), and a AMED grant (Number JP21zf0127004).

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Keywords: circadian rhythm, diabetes mellitus, hypertension, left ventricular hypertrophy, pharmacology

Main text:

Hypertension and diabetes mellitus (DM) are independent and established risk factors for cardiovascular diseases, including left ventricular hypertrophy (LVH), congestive heart failure, stroke, coronary artery disease and peripheral artery disease [1]. Cardiovascular diseases share common pathogenic mechanisms, including inflammation and oxidative stress [1]. Hypertension and DM synergistically promote these mechanisms in a vicious cycle [1]. LVH occurs as an adaptive response to pathological stress in the early stage of functional and structural changes of the heart, called cardiac remodeling [2]; LVH is used as a potent predictor of cardiovascular events [3].

Blood pressure (BP) exhibits a circadian rhythm that is regulated by the intrinsic rhythm of clock genes through controlling the neurohumoral and autonomic nervous systems [4]. In healthy subjects, BP dips at night during rest, undergoes a steep increase in the morning, and peaks in the afternoon; nighttime BP decreases by 10-20% of daytime BP, which is called normal dipper pattern [4]. The impact of diurnal BP variation on cardiovascular events has been vigorously investigated. Accumulating evidence has demonstrated that nighttime BP is a stronger predictor of clinical outcomes than either daytime or clinic BP [4]. Controlling nighttime BP is one of important challenges in cardiovascular medicine.

Nocturnal hypertension (NH) is defined as systolic BP >120mHg and/or diastolic BP >70mmHg at night [4]. Several mechanisms have been suggested to contribute to the pathogenesis of NH: increase in salt sensitivity and high-salt diet, autonomic nervous dysfunction leading to sympathetic hyperactivity, and advanced structural disease such as vascular resistance and arterial stiffness [4]. Hyperinsulinemia and hyperglycemia in DM have been shown to enhance these mechanisms [1]. NH has been shown to be associated with the risk of LVH in patients with DM

[5]. DM patients are a heterogenous population across glucose control status and medication use. It remains largely unknown whether this heterogeneity affects the impact of NH on cardiovascular outcomes.

In this issue of Hypertension Research, Toriumi et al. provided intriguing information on the impact of NH and DM on LVH [6]. The authors analyzed the data of 1,277 patients, who underwent both ambulatory BP monitoring and echocardiography, from the Japan Morning Surge-Home Blood Pressure (J-HOP) study, a prospective observational study of 4,310 Japanese individuals who had a history of or risk factors for cardiovascular disease [7]. In this cross-sectional analysis of the J-HOP study population, they found that inadequate control of nighttime systolic BP is associated with the presence of LVH after adjustment for age, body mass index, use of antihypertensive drugs, office systolic BP and DM, whereas the presence of inadequately controlled daytime systolic BP or DM did not increase the risk of LVH after multivariate analysis. When the authors divided the population into 3 groups, such as non-diabetic, adequately controlled diabetic and poorly controlled diabetic groups, poorly controlled nighttime systolic BP increased the risk of LVH only in the poorly controlled diabetic group. A comparable risk of LVH was observed among the 3 groups with adequately controlled nighttime systolic BP. Although causality cannot be determined due to the study design, these findings suggest that NH and DM might synergistically promote cardiac remodeling when both of them are under poor control. This study supports clinical significance of NH as a therapeutic target for cardiovascular disease in diabetic patients.

High BP imposes mechanical stress on the heart, and causes LVH through promoting cardiac inflammation and oxidative stress (Fig. 1) [2]. In this study, NH did not increase the risk of LVH in non-diabetic individuals or adequately controlled diabetic patients, suggesting that high

nighttime BP itself might not be sufficient to cause LVH. Indeed, the cutoff BP threshold of NH is lower than that of daytime hypertension. NH might represent its underlying mechanisms including sympathetic hyperactivity, rather than mechanical stress, as a risk factor for LVH. Similarly, inadequately controlled DM patients without NH did not have the higher risk of LVH than non-diabetic individuals, indicating that hyperglycemia alone might not be a strong trigger of cardiac remodeling. In DM, a wide array of pathophysiological processes, including inflammation, oxidative stress and altered insulin signaling, contributes to the development of LVH [8]. Sympathetic hyperactivity, reflected by NH, might synergistically exacerbate these pathogenic mechanisms in DM. Indeed, it was reported that sympathetic activation plays an essential role in cardiac inflammation and oxidative stress [2]. It would be interesting to examine whether inadequately controlled DM patients with nighttime systolic BP ranging from 120mmHg to 135mmHg would have the higher risk of LVH than those without NH and how the risk of LVH in this subpopulation of NH compares with that in patients with nighttime systolic BP above 135mmHg, the cutoff threshold of daytime hypertension. In addition, it would be of great importance to investigate whether NH remains an independent risk factor for LVH in poorly controlled DM patients after adjustment for indicators of autonomic function, including nighttime heart rate variability. Furthermore, detailed assessment of insulin resistance, proinflammatory cytokine expression and oxidative stress with blood and urine tests would provide mechanistic insights into how the heterogeneity of DM affects the impact of NH on the development of LVH.

NH is closely associated with increased circulating volume due to high salt sensitivity and sleeping in the supine position and hyperactivation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system [4]. Consistently, diuretics, RAAS inhibitors and sympatholytics, as well as calcium channel blockers (CCBs), have been reported to be effective

for reducing nighttime BP [4]. Interestingly, it has been suggested that each class of antihypertensive drugs might have different nighttime BP-lowering profiles [4]. For example, the nighttime BP-lowering effect of controlled-release nifedipine, a CCB, at the dose of 40mg was shown to be stronger than that of carvedilol, a β-blocker, at the dose of 20mg with bedtime administration, while carvedilol, but not nifedipine, significantly reduced a nighttime BP surge induced by hypoxia [9]. In DM patients, diuretics or β-blockers might exacerbate glucose control status. It would be of great importance to examine the impact of antihypertensive drug classes or nighttime BP-lowering profiles on target organ damage, including LVH, in DM patients in prospective studies. Furthermore, since insomnia is associated with DM and NH [4], it would be interesting to investigate the effect of melatonin receptor antagonists or orexin receptor blockers on nighttime BP control and clinical outcomes in DM patients.

Some classes of antidiabetic drugs have been reported to protect against cardiac remodeling. The MET-REMODEL trial showed that a biguanide drug, metformin, significantly reduced left ventricular mass (LVM) indexed to height, office systolic BP, body weight and oxidative stress after 12 months of treatment in patients without type 2 DM who have coronary artery disease with insulin resistance and/or pre-diabetes, compared with placebo [10]. Metformin has been suggested to reduce cardiac hypertrophy by inhibiting inflammation and oxidative stress and improving mitochondrial function mainly through AMP-activated protein kinase (AMPK)-dependent mechanism [8]. The DAPA-LVH trial demonstrated that the addition of the sodium-glucose cotransporter 2 (SGLT2) inhibitor dapagliflozin to standard treatment in patients with type 2 DM, LVH and controlled BP was associated with a significant regression of LVM assessed by cardiac MRI after a mean treatment period of 12 months, compared with placebo [11]. Interestingly, dapagliflozin reduced nighttime systolic BP. The EMPA-HEART Cardiolink-6 trial showed that

6-month treatment with the SGLT2 inhibitor empagliflozin induces significant LVM regression in patients with type 2 DM and coronary artery disease [12]. Accumulating evidence has shown that SGLT2 inhibitors suppress inflammation, oxidative stress and sympathetic activity and maintain mitochondrial function [13]. Further studies are warranted to examine the impact of antidiabetic drugs on NH and LVH in both uncontrolled and controlled DM patients.

Antihypertensive drugs are usually administered in the morning. Since NH is an important predictor of cardiovascular outcomes, it has been hypothesized that taking antihypertensive drugs in the evening might improve clinical outcomes, considering pharmacokinetics. On the other hand, evening dosing might reduce drug adherence, compared with morning dosing [14]. The timing of their administration remains controversial. The Treatment in Morning versus Evening (TIME) study, a prospective, randomized, open-label, blind-endpoint clinical trial, demonstrated that evening dosing of antihypertensive drugs was not different from morning dosing in terms of major cardiovascular outcomes or mortality [15]. However, the TIME study did not examine nighttime BP or diurnal BP variation. It remains unclear whether the timing of administration of antihypertensive drugs would affect nighttime BP control and clinical outcomes in patients with NH or disorders of diurnal BP variation. In addition, it is unelucidated whether evening or nighttime dosing of antihypertensive drugs would improve cardiovascular events in uncontrolled DM patients, who were susceptible to NH in this study. Further studies will be necessary to identify the subpopulation who benefits from chronotherapy, the scheduled drug administration based on individual's circadian rhythm.

In conclusion, nighttime systolic BP might be associated with the risk of LVH in individuals with poorly controlled DM, but not in individuals with adequately controlled DM. Further studies are needed to elucidate the underlying mechanisms and to clarify the optimal

medications and timing of their administration in uncontrolled DM patients with NH.

Acknowledgments

YH is supported by research grants from the Vehicle Racing Commemorative Foundation, the Takeda Science Foundation and the Mitsui Sumitomo Insurance Welfare Foundation, and a JSPS KAKENHI grant (Number JP23K07501). MS is supported by a research grant from the Vehicle Racing Commemorative Foundation, a JSPS KAKENHI grant (Number JP22H03069), and a AMED grant (Number JP21zf0127004).

Conflict of interest

MS has received speaking honoraria from Bayer Yakuhin, Ltd., Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Company, Ltd., Daiichi Sankyo Company, Ltd., and Nippon Boehringer Ingelheim Company, Ltd., and clinical research funding from Bayer Yakuhin, Ltd. The other authors declare no conflicts of interest.

References

1. Liu W, Higashikuni Y, Sata M. Optimizing antihypertensive therapy in patients with diabetes mellitus. Hypertens Res. 2023;46:797-800.
2. Higashikuni Y, Liu W, Numata G, Tanaka K, Fukuda D, Tanaka Y, et al. NLRP3 Inflammasome Activation Through Heart-Brain Interaction Initiates Cardiac Inflammation and Hypertrophy During Pressure Overload. Circulation. 2023;147:338-355.
3. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med. 1990;322:1561-1566.
4. Kario K. Nocturnal Hypertension: New Technology and Evidence. Hypertension. 2018;71:997-1009.
5. Felicio JS, Pacheco JT, Ferreira SR, Plavnik F, Moises VA, Kohlmann O, Jr., et al. Hyperglycemia and nocturnal systolic blood pressure are associated with left ventricular hypertrophy and diastolic dysfunction in hypertensive diabetic patients. Cardiovasc Diabetol. 2006;5:19. doi: 10.1186/1475-2840-5-19.
6. Toriumi S, Hoshide S, Kabutoya T, Kario K. Nighttime blood pressure and glucose control impacts on left ventricular hypertrophy: The Japan Morning Surge Home Blood Pressure (J-HOP) study. Hypertens Res. (in press)
7. Hoshide S, Yano Y, Haimoto H, Yamagiwa K, Uchiba K, Nagasaka S, et al. Morning and Evening Home Blood Pressure and Risks of Incident Stroke and Coronary Artery Disease in the Japanese General Practice Population: The Japan Morning Surge-Home Blood Pressure Study. Hypertension. 2016;68:54-61.
8. Mohan M, Dihoum A, Mordi IR, Choy AM, Rena G, Lang CC. Left Ventricular

Hypertrophy in Diabetic Cardiomyopathy: A Target for Intervention. Front Cardiovasc Med. 2021;8:746382. doi: 10.3389/fcvm.2021.746382.

9. Kario K, Kuwabara M, Hoshide S, Nagai M, Shimpo M. Effects of nighttime single-dose administration of vasodilating vs sympatholytic antihypertensive agents on sleep blood pressure in hypertensive patients with sleep apnea syndrome. J Clin Hypertens (Greenwich). 2014;16:459-466.

10. Mohan M, Al-Talabany S, McKinnie A, Mordi IR, Singh JSS, Gandy SJ, et al. A randomized controlled trial of metformin on left ventricular hypertrophy in patients with coronary artery disease without diabetes: the MET-REMODEL trial. Eur Heart J. 2019;40:3409-3417.

11. Brown AJM, Gandy S, McCrimmon R, Houston JG, Struthers AD, Lang CC. A randomized controlled trial of dapagliflozin on left ventricular hypertrophy in people with type two diabetes: the DAPA-LVH trial. Eur Heart J. 2020;41:3421-3432.

12. Verma S, Mazer CD, Yan AT, Mason T, Garg V, Teoh H, et al. Effect of Empagliflozin on Left Ventricular Mass in Patients With Type 2 Diabetes Mellitus and Coronary Artery Disease: The EMPA-HEART CardioLink-6 Randomized Clinical Trial. Circulation. 2019;140:1693-1702.

13. Vaziri Z, Saleki K, Aram C, Alijanizadeh P, Pourahmad R, Azadmehr A, Ziaei N. Empagliflozin treatment of cardiotoxicity: A comprehensive review of clinical, immunobiological, neuroimmune, and therapeutic implications. Biomed Pharmacother. 2023;168:115686. doi: 10.1016/j.biopha.2023.115686.

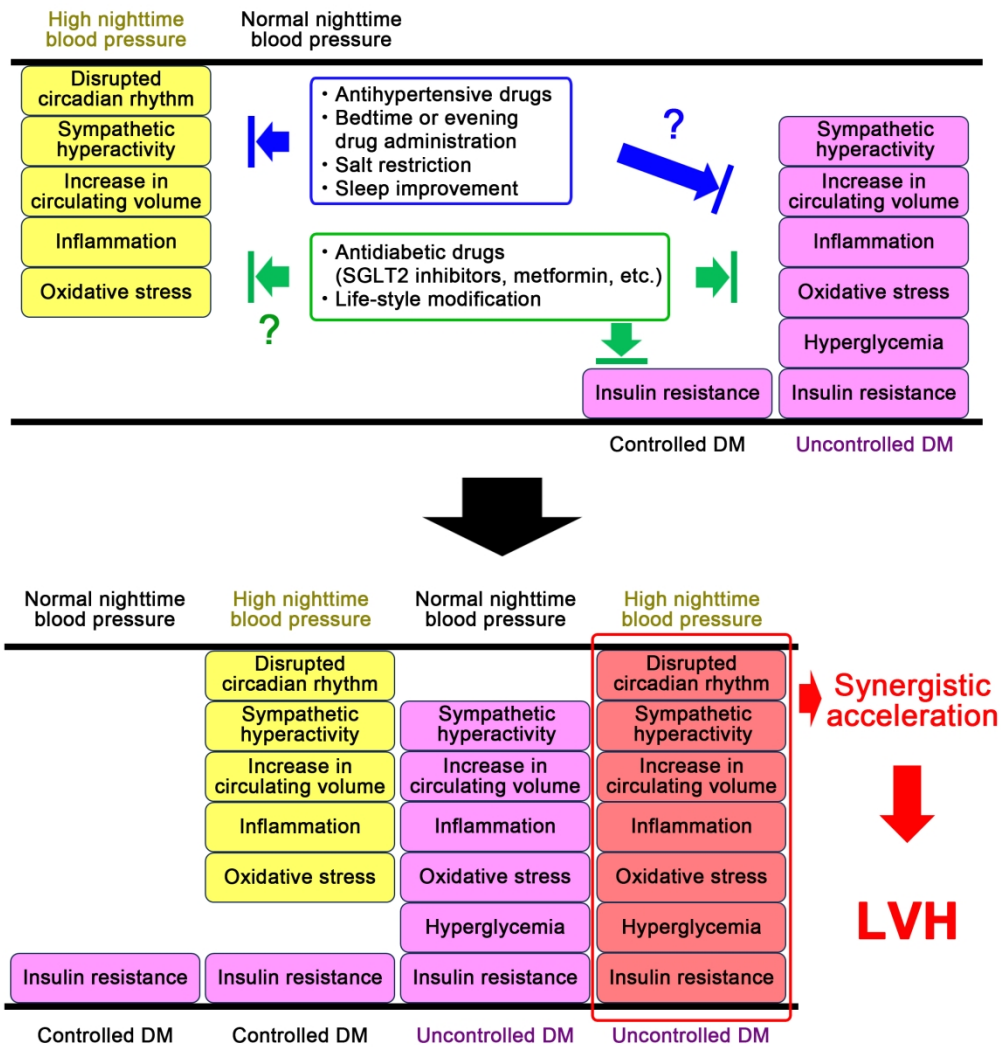
14. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing

histories. BMJ. 2008;336:1114-1117.

15. Mackenzie IS, Rogers A, Poulter NR, Williams B, Brown MJ, Webb DJ, et al. Cardiovascular outcomes in adults with hypertension with evening versus morning dosing of usual antihypertensives in the UK (TIME study): a prospective, randomised, open-label, blinded-endpoint clinical trial. Lancet. 2022;400:1417-1425.

Figure legend

Fig. 1 Potential mechanisms underlying the high risk of left ventricular hypertrophy (LVH) in patients with high nighttime blood pressure and uncontrolled diabetes mellitus (DM). Nocturnal hypertension and DM share common pathogenic mechanisms, such as inflammation, oxidative stress, increase in circulating volume, and sympathetic hyperactivity. In controlled DM patients with nocturnal hypertension or uncontrolled DM patients with normal nighttime blood pressure, these common mechanisms might be triggered by either nocturnal hypertension or uncontrolled DM alone. In uncontrolled DM patients with nocturnal hypertension, both high nighttime blood pressure and poor DM control might synergistically drive these common mechanisms, which might aggravate nocturnal hypertension and DM in a vicious cycle. As a result, the development of LVH might be accelerated in this subpopulation. The optimal therapeutic strategies for LVH regression in this subpopulation remain unelucidated. SGLT2, sodium-glucose cotransporter 2.



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