

Association of lower nighttime diastolic blood pressure and hypoxia with silent myocardial injury: The Japan Morning Surge-Home Blood Pressure study

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Abstract

Whether marked nocturnal blood pressure (BP) reduction is associated with cardiovascular disease (CVD) is still controversial. In addition, no report has yet discussed the relationship between lower nocturnal BP and CVD, involving modification by nighttime hypoxia. We evaluated 840 patients who had one or more cardiovascular risk factors by measuring their high-sensitivity cardiac troponin T (Hs-cTnT), N-terminal pro-B-type natriuretic peptide (NT-pro BNP), and nighttime saturation levels and performing ambulatory BP monitoring. The lowest tertile in nighttime diastolic BP (DBP) (≤ 66 mmHg) had increased likelihood of the presence of ≥ 0.014 ng/ml of Hs-cTnT compared with the second tertile (odds ratio [OR] 1.91, 95% confidence interval [CI] 1.01–3.63), and the lowest tertile of minimum blood oxygen saturation ($\leq 81\%$) had increased likelihood of the presence of ≥ 0.014 ng/ml of Hs-cTnT compared with the third tertile (OR 2.15, 95% CI 1.13–4.10). Additionally, the patients with both lowest tertile of nighttime DBP and minimum SpO₂ showed increased likelihood of the presence of ≥ 0.014 ng/ml of Hs-cTnT compared with those without this combination (OR 2.93, 95% CI 1.40–6.16). On the other hand, these associations were not found in the presence of ≥ 125 pg/ml of NT-pro BNP. In the clinical population, each of lower nocturnal DBP and nighttime hypoxia was associated with asymptomatic myocardial injury, which was represented as higher Hs-cTnT, and coexisting lower nocturnal DBP and nighttime hypoxia had an additive effect on the risk of myocardial injury.

1 | INTRODUCTION

Elevated blood pressure (BP), when assessed by not only conventional office BP but also out-of-office BP measurements, such as ambulatory BP monitoring (ABPM), has been well acknowledged to be a cardiovascular disease (CVD) risk.^{1–4} In particular, elevated nighttime BP as assessed by ABPM has been associated with myocardial overload and

has been shown to have more prognostic power than daytime BP.^{5–13} On the other hand, excessive nighttime BP reduction may also be a CVD risk. Previous studies reported that marked nocturnal BP fall, that is, extreme-dipping, was associated with a risk of cerebral and myocardial ischemia,^{14–18} but this issue is still controversial.

Nighttime hypoxia induced by sleep-disordered breathing (SDB) has also been revealed to confer a risk of CVD events.^{19–21} Various

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pathological conditions, such as increased sympathetic nerve activity, inflammation, and vascular endothelial dysfunction, have been suggested to be involved in the mechanisms underlying the association between SDB and CVD events.²² From the perspective of hemodynamics, dramatic surges in arterial BP due to peripheral vasoconstriction and increased cardiac output, and simultaneous hypoxemia and increased myocardial oxygen demand may promote nocturnal myocardial ischemia.²³

High-sensitivity cardiac troponin T (Hs-cTnT) assays can detect asymptomatic myocardial injury and have been strongly predictive of fatal and nonfatal CVD events in numerous observational studies.^{24–26} On the other hand, N-terminal pro-B-type natriuretic peptide (NT-pro BNP) is a representative biomarker secreted mainly from the ventricles in response to volume expansion and pressure overload.²⁷

Accordingly, we hypothesized that lower nighttime DBP assessed by ABPM and nighttime hypoxia may be associated with the elevation of Hs-cTnT and investigated whether this association exists in patients with myocardial overload, as assessed by NT-pro BNP levels. We further hypothesized that coexisting lower nighttime DBP and nighttime hypoxia may have an additive effect on the association with Hs-cTnT, because a majority of previous studies focused on the association of either lower nighttime BP or hypoxia with myocardial injury and there have been no reports investigating whether the association between lower nighttime BP and myocardial injury is modified by nighttime hypoxia.

Here, we investigated the association between nighttime BP and nighttime hypoxia, singly or in combination, and each of Hs-cTnT or NT-pro BNP in a clinical population with one or more cardiovascular risk factors.

2 | METHODS

2.1 | Patients

This study was a post hoc analysis of the J-HOP study (Japan Morning Surge-Home Blood Pressure). Details of the J-HOP study rationale, design, and procedures have been published.²⁸ Between 2005 and 2012, the J-HOP study enrolled 4310 patients with a history of or risk factors for CVD and followed them up through March 2015. The CVD risk factors were as follows: hypertension, hyperlipidemia, diabetes (fasting blood sugar 126 mg/dl and/or current use of an antidiabetic drug), glucose intolerance, metabolic syndrome, chronic kidney disease (estimated glomerular filtration rate <60 ml/min/1.73 m²), history of CVD (coronary artery disease, stroke, aortic dissection, peripheral artery disease, congestive heart failure), atrial fibrillation, current smoking, chronic obstructive pulmonary disease, or sleep apnea syndrome. We excluded patients who had malignancy or chronic inflammatory disease. The Institutional Review Boards of Jichi Medical University School of Medicine approved the methods, and all of the patients provided written informed consent to participate and to have their data published.

The present study included 840 patients in whom Hs-cTnT, NT-pro BNP, ABPM and nighttime SpO₂ levels were examined at baseline in the J-HOP study.

2.2 | ABPM

Ambulatory blood pressure monitoring was performed using a validated device: either TM-2421 or TM-2425 (A&D).²⁹ Measurements were taken at 30-min intervals for 24 h on a weekday.^{30,31} The appropriate cuff size for individual arm circumference was used. Awake and sleeping periods were defined according to the records in the patient diaries. Nighttime BP was calculated as the average of the BP values from the time that the patient went to bed until the time of awakening, and daytime BP was defined as the average BP recorded during the rest of the day. Patients were considered to have adequate ABPM if they had ≥ 10 awake and ≥ 5 asleep systolic BP (SBP) and diastolic BP (DBP) measurements.

2.3 | Oxygen measurement

SpO₂ was detected using a portable pulse oximeter (PULSOX-Me300; Konica-Minolta) in parallel with ABPM. Patients were instructed to wear the pulse oximeter at bedtime and remove it when waking up. The finger probe of the portable oximeter was positioned on the patient's hand on the side opposite to the arm wearing the BP cuff, and the body of portable oximeter was attached to the patient's wrist during nighttime (Figure S1). SpO₂ and the pulse rate waveform were recorded every second. All data in the pulse oximeter device were downloaded to a computer and sent to the study control center (Jichi Medical University).

2.4 | Laboratory examination

Blood samples were collected upon each patient's hospital arrival in the morning in a fasting state at enrollment and at the end of the study. The blood samples were centrifuged at 3000 g for 15 min at room temperature. Plasma/serum samples after separation were stored at 4°C in refrigerated containers and sent to a commercial laboratory (SRL) within 24 h. All assays were performed within 24 h of arrival of the samples at this single laboratory center. Using the stored serum samples, Hs-cTnT was measured using a highly sensitive assay on an automated platform (ElecSys-2010 Troponin T hs STAT; Roche Diagnosis), with a lower detection limit of 0.003 ng/ml and a reported 99th percentile value in apparently healthy individuals of 0.014 ng/ml.³² Serum NT-pro BNP levels were determined using a chemiluminescence immunoassay kit (Roche Diagnostics). The lower limit of detection of NT-pro BNP is 5 pg/ml. The cutoff point (125 pg/ml) for NT-pro BNP followed the diagnostic criteria for suspected heart failure in the European

Society of Cardiology heart failure guidelines.³³ The intra/inter-coefficients of variation were 2.02%/3.02% for Hs-cTnT and 1.93%/3.13% for NT-pro BNP.

2.5 | Echocardiography

Echocardiography was performed at each participating institute. The two-dimensional M-mode or B-mode image was recorded using an ultrasound machine according to the guidelines of the American Society of Echocardiology and the European Association of Echocardiography.³⁴ The left ventricular mass (LVM) was obtained using the formula validated by the American Society of Echocardiology: $LVM = 0.8 \times (1.04 [(LVIDd + PWTd + SWTd)^3 - (LVIDd)^3]) + 0.6$ g, where LVIDd is LV internal diameter in diastole, PWTd is posterior wall thickness in diastole, and SWTd is septal wall thickness in diastole. LVM index (LVMI) was calculated as LVM/body surface area. These measurements were based on the guidelines of the American Society of Echocardiology and the European Association of Echocardiography.³⁴

2.6 | Statistical analysis

The data were expressed as the mean \pm SD or a percentage. Continuous and categorical variables were compared between groups using Student's *t*-test and the chi-squared test, respectively. The likelihood of the presence of ≥ 0.014 ng/ml of Hs-cTnT and ≥ 125 pg/ml of NT-pro BNP by tertiles of BP parameters and minimum SpO₂ was analyzed by multivariable logistic regression analysis after adjusting for confounding factors, which were determined by the difference in variables between the groups with and without ≥ 0.014 ng/ml of Hs-cTnT or with and without ≥ 125 pg/ml of NT-pro BNP. In this analysis, we selected the tertile of the lowest prevalence of ≥ 0.014 ng/ml of Hs-cTnT or ≥ 125 pg/ml of NT-Pro BNP as a reference. One-way analysis of variance was performed to detect difference in LVMI among tertile groups. In addition, multivariable logistic regression analysis was performed in four groups (with/without the lowest tertile of nighttime DBP and with/without the lowest tertile of minimum SpO₂) after adjusting for the confounding factors mentioned above. All statistical analyses were performed with STATA version 12.1 (STATA Corp). *p*-values $< .05$ were considered significant for all tests.

3 | RESULTS

Patient characteristics are summarized in Table 1. Of 840 patients, 50.4% were male. 19.2% of the patients had a past history of CVD and 81.8% of the patients had received antihypertensive medication. There were 86 patients (10.2%) with Hs-cTnT ≥ 0.014 ng/ml and 194 patients (23.1%) with NT-pro BNP ≥ 125 pg/ml, respectively.

Table 2 describes the association between tertiles according to daytime DBP, nighttime DBP, SpO₂ $< 90\%$ and minimum SpO₂ and

TABLE 1 Characteristics of all patients

	n = 840
Age, years	64.3 \pm 11.0
Male, %	50.4
BMI, kg/m ²	24.5 \pm 3.5
Smoking, %	11.8
Alcohol, %	20.6
Diabetes, %	29.0
Dyslipidemia, %	34.0
Past history of CVD, %	19.2
eGFR, ml/min/1.73 m ²	73.3 \pm 17.9
Antihypertensive drug, %	81.8
Calcium antagonist	51.0
ACE inhibitor	7.3
ARB	50.1
Alfa blocker	7.4
Beta blocker	16.0
Diuretics	24.5
BP parameters, mmHg	
Daytime SBP	136.1 \pm 13.5
Daytime DBP	80.1 \pm 9.7
Nighttime SBP	121.5 \pm 14.6
Nighttime DBP	71.0 \pm 9.2
SpO ₂ parameters	
Mean SpO ₂ , %	95.5 \pm 1.9
Median SpO ₂ , %	95.7 \pm 1.8
3% ODI, number	7.9 \pm 8.7
Total time SpO ₂ $< 90\%$, min	2.2 \pm 6.6
Minimum SpO ₂ , %	83.8 \pm 6.9
Biomarkers	
Presence of ≥ 0.014 ng/ml of Hs-cTnT, %	10.2
Presence of ≥ 125 pg/ml of NT-pro BNP, %	23.1

Note: Data are mean \pm SD or percentage.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; Hs-cTnT, high sensitive cardiac troponin T; NT-pro BNP, N-terminal pro-B-type natriuretic peptide; ODI, oxygen desaturation index; SBP, systolic blood pressure; SpO₂, saturation of percutaneous oxygen.

the presence of ≥ 0.014 ng/ml of Hs-cTnT. The proportion of those with ≥ 0.014 ng/ml was significant in tertiles of all groups. When the tertile group of the lowest proportion was defined as the reference in each group, the lowest tertile in nighttime DBP (48–66 mmHg) and minimum SpO₂ (54%–81%) were significantly associated with the presence of ≥ 0.014 ng/ml of Hs-cTnT (odds ratio [OR] of the lowest tertile of nighttime DBP, 1.91; 95% CI, 1.01–3.63; OR of the lowest tertile of minimum SpO₂, 2.15; 95% CI, 1.13–4.10) after adjustment for age, past history of CVD, estimated glomerular filtration rate (eGFR), and use of angiotensin II receptor blockers (ARBs), alpha

TABLE 2 Association between BP parameters or SpO₂ parameters and the presence of ≥ 0.014 ng/ml of Hs-cTnT

	Daytime SBP		
	Tertile 1	Tertile 2	Tertile 3
Range, mmHg	103–129	130–140	141–197
Presence of ≥ 0.014 ng/ml of Hs-cTnT/number	32/263	25/290	29/287
Prevalence, %	12.17	8.62	10.10
OR (95% CI)	1.32 (0.73–2.41)	1 (Reference)	1.30 (0.70–2.41)
	Daytime DBP		
	Tertile 1	Tertile 2	Tertile 3
Range, mmHg	56–74	75–84	85–121
Presence of ≥ 0.014 ng/ml of Hs-cTnT/number	38/254	30/301	18/285
Prevalence, %	14.96	9.97	6.32
OR (95% CI)	1.48 (0.74–2.94)	1.24 (0.64–2.41)	1 (Reference)
	Nighttime SBP		
	Tertile 1	Tertile 2	Tertile 3
Range, mmHg	88–113	114–125	126–188
Presence of ≥ 0.014 ng/ml of Hs-cTnT/number	26/263	27/278	33/299
Prevalence, %	9.89	9.71	11.04
OR (95% CI)	1.21 (0.65–2.26)	1 (Reference)	1.07 (0.59–1.96)
	Nighttime DBP		
	Tertile 1	Tertile 2	Tertile 3
Range, mmHg	48–66	67–73	74–109
Presence of ≥ 0.014 ng/ml of Hs-cTnT/number	40/271	21/260	25/309
Prevalence, %	14.76	8.08	8.09
OR (95% CI)	1.91 (1.01–3.63)	1 (Reference)	1.27 (0.65–2.49)
	Minimum SpO ₂		
	Tertile 1	Tertile 2	Tertile 3
Range, %	54–81	82–87	88–97
Presence of ≥ 0.014 ng/ml of Hs-cTnT/number	38/250	30/298	18/292
Prevalence, %	14.63	9.52	5.88
OR (95% CI)	2.15 (1.13–4.10)	1.61 (0.83–3.12)	1 (Reference)

Abbreviations: BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; Hs-cTnT, high sensitive cardiac troponin T; OR, odds ratio; SBP, systolic blood pressure; SpO₂, saturation of percutaneous oxygen.

blockers, beta blockers, and diuretics, which showed significant differences between the groups with/without Hs-cTnT ≥ 0.014 ng/ml (Table S1).

Table 3 shows the association between tertiles according to daytime DBP, nighttime DBP, SpO₂ < 90% and minimum SpO₂ and the presence of ≥ 125 pg/ml of NT-pro BNP. The proportion of those with ≥ 125 ng/ml was significant in all tertile groups. When the tertile group with the lowest proportion was defined as the reference in each group, the lowest tertile in daytime SBP (103–129 mmHg) and highest tertile in nighttime SBP (126–188 mmHg) were significantly associated with the presence of ≥ 125 pg/ml of NT-pro BNP (OR of the lowest tertile of daytime SBP, 1.61; 95% CI, 1.04–2.50; OR of the highest tertile of nighttime SBP, 1.63; 95% CI, 1.03–2.57)

after adjustment for age, sex, past history of CVD, eGFR, and use of angiotensin-converting enzyme inhibitors, ARBs, alpha blockers, beta blockers, and diuretics, which showed significant differences between the group with and that without ≥ 125 pg/ml of NT-pro BNP (Table S2). In our present study, daytime and nighttime SBP was associated with LVMI, but this association was not found in DBP and minimum SpO₂ (Table S3).

Next, we divided the individuals into four groups according to the lowest tertile of nighttime DBP or other tertiles and the lowest tertile of minimum SpO₂ or other tertiles. The group with the lowest tertile of nighttime DBP and minimum SpO₂ had a significant risk of the presence of ≥ 0.014 ng/ml of Hs-cTnT compared with the group with other tertiles of nighttime DBP and minimum SpO₂. The chart

TABLE 3 Association between BP parameters or SpO₂ parameters and the presence of ≥ 125 pg/ml of NT-pro BNP

	Daytime SBP		
	Tertile 1	Tertile 2	Tertile 3
Range, mmHg	103–129	130–140	141–197
Presence of ≥ 125 pg/ml of NT-Pro BNP/ number	75/263	55/290	64/287
Prevalence, %	28.52	18.97	22.30
OR (95% CI)	1.61 (1.04–2.50)	1 (Reference)	1.53 (0.97–2.40)
	Daytime DBP		
	Tertile 1	Tertile 2	Tertile 3
Range, mmHg	56–74	75–84	85–121
Presence of ≥ 125 pg/ml of NT-Pro BNP/ number	91/254	59/301	44/285
Prevalence, %	35.83	19.60	15.44
OR (95% CI)	1.58 (0.98–2.54)	0.92 (0.57–1.49)	1 (Reference)
	Nighttime SBP		
	Tertile 1	Tertile 2	Tertile 3
Range, mmHg	88–113	114–125	126–188
Presence of ≥ 125 pg/ml of NT-Pro BNP/ number	49/263	63/278	82/299
Prevalence, %	9.19	21.63	28.00
OR (95% CI)	1 (Reference)	1.18 (0.74–1.88)	1.63 (1.03–2.57)
	Nighttime DBP		
	Tertile 1	Tertile 2	Tertile 3
Range, mmHg	48–66	67–73	74–109
Presence of ≥ 125 pg/ml of NT-Pro BNP/ number	76/271	61/260	57/309
Prevalence, %	28.04	23.46	18.45
OR (95% CI)	1.02 (0.65–1.61)	1.03 (0.65–1.63)	1 (Reference)
	Minimum SpO ₂		
	Tertile 1	Tertile 2	Tertile 3
Range, %	54–81	82–87	88–97
Presence of ≥ 125 pg/ml of NT-Pro BNP/ number	60/250	69/298	65/292
Prevalence, %	24.39	23.17	21.43
OR (95% CI)	0.75 (0.48–1.19)	0.86 (0.56–1.32)	1 (Reference)

Abbreviations: BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; NT-pro BNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio; SBP, systolic blood pressure; SpO₂, saturation of percutaneous oxygen.

of Figure focuses on the two parameters, nighttime DBP and minimum SpO₂ (OR, 2.93; 95% CI, 1.40–6.16; Figure 1).

4 | DISCUSSION

The main findings of the present study can be summarized as follows: (1) Lower nighttime DBP (≤ 66 mmHg) was associated with asymptomatic

myocardial injury, which was represented as higher Hs-cTnT. (2) Lower minimum SpO₂ ($\leq 81\%$) during nighttime was also associated with asymptomatic myocardial injury. In addition, the patients with both lower nighttime DBP and minimum nighttime SpO₂ had approximately threefold greater risk for the presence of asymptomatic myocardial injury compared with those who did not have both lower nighttime DBP and minimum SpO₂. To the best of our knowledge, this is the first study to show that coexisting lower nocturnal DBP and nighttime hypoxia

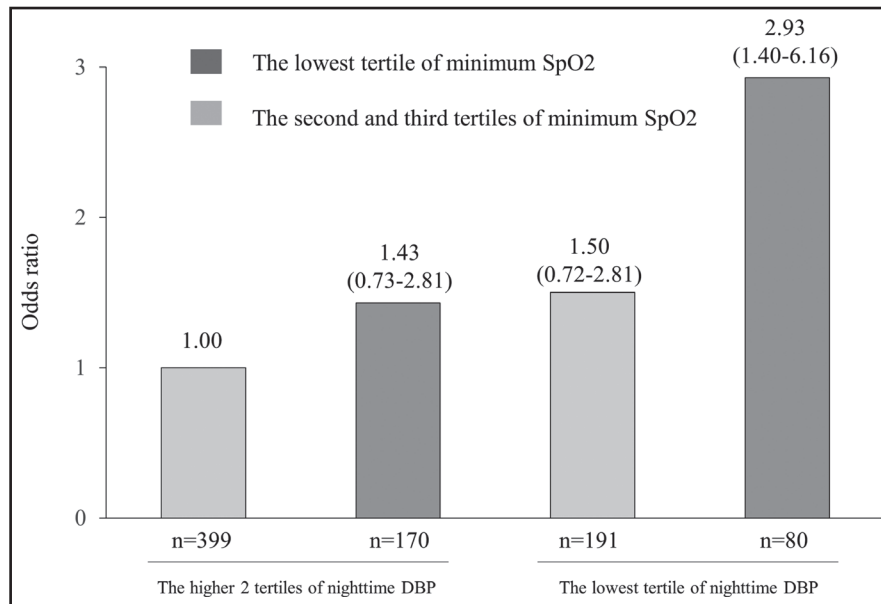


FIGURE 1 Association between nighttime DBP or minimum SpO₂ and the presence of ≥ 0.014 ng/ml of Hs-cTnT

had additive effects on the risk of myocardial injury when patients with both these parameters were compared to those without.

4.1 | Nighttime DBP and asymptomatic myocardial injury

In this study, lower DBP during nighttime (≤ 66 mmHg) was associated with asymptomatic myocardial injury, but lower BP during daytime was not associated with asymptomatic myocardial injury.

Although several studies have reported that increased nighttime BP was associated with CVD incidence and had greater prognostic power compared with daytime BP,^{5,6,8,9,12} whether lower BP during nighttime is harmful for the management of hypertension remains an ongoing debate. Initially, in elderly non-treated hypertensive patients, patients with extreme-dipping, defined as an excessive nocturnal BP fall $>20\%$, were reported to be at higher risk of stroke incidence compared with those with regular dipping, defined as a normal nocturnal BP fall of 10% – 20% .¹⁶ Interestingly, Pierdomenico and colleagues performed ambulatory BP and electrocardiographic (ECG) monitoring simultaneously in 70 untreated hypertensive patients with stable significant coronary artery stenosis on selective coronary arteriography (considered present when there was $\geq 70\%$ diameter narrowing of a major coronary vessel or $\geq 50\%$ narrowing of the left main stem) and demonstrated that the patients with extreme-dipping of DBP (62 ± 3 mmHg) after antihypertensive therapy showed a significant increase of nighttime ischemia episodes, defined as horizontal or down-sloping ST-segment change on ECG.¹⁵ Our findings would support the results of these previous studies, indicating that excessive nighttime BP reduction may lead to organ injury. On the other hand, a study using the international ABPM database (IDACO), which is made up of individuals from the general

population, showed that extreme-dipping of DBP (average nighttime DBP, 60 ± 7 mmHg) conferred an increased risk of CVD events compared with dipping in those without antihypertensive treatment, whereas this association was not found in those with antihypertensive treatment.⁷ The discrepancy between the previous studies and our present investigation may be explained by differences in the populations. Namely, our patients had more than one CVD risk, whereas the patients studied by Pierdomenico and colleagues and Boggia and colleagues had only one or no risk factor. However, like Pierdomenico and colleagues, we also found that extreme nighttime BP fall may confer a risk of organ damage in high risk populations.

Our findings showed that lower nighttime DBP was associated with asymptomatic myocardial injury, but nighttime SBP was not. Coronary artery inflow primarily occurs during diastolic phase.³⁵ Additionally, it has been reported that low DBP can reduce coronary blood flow and cause myocardial ischemia, especially in the subendocardium.³⁶ A reduction of coronary flow results from increased coronary tone and vasospasm,^{37,38} and may cause an imbalance between myocardial oxygen supply and myocardial oxygen demand, resulting in nighttime ischemia. Amah and colleagues showed a significantly lower subendocardial viability ratio (diastolic pressure-time index [ie, available coronary blood supply]/systolic pressure-time index [ie, myocardial blood demand] ratio) in extreme-dippers than in dippers,³⁹ which corresponded to impaired subendocardial flow.^{40,41}

4.2 | Nighttime hypoxia and asymptomatic myocardial injury

Our study showed that lower minimum SpO₂ ($\leq 81\%$) was associated with asymptomatic myocardial injury. To our knowledge, our study is the first report to show that minimum SpO₂ is directly

related to myocardial injury. Nocturnal SpO₂ reduction is a sensitive marker indicating the severity of intermittent hypoxia associated by SDB, and pathological mechanisms such as oxidative stress, systemic, and vascular inflammation, vasoconstriction and elevated BP lead to endothelial dysfunction, which in turn leads to CVD development.^{19–21,42} Various parameters are used for evaluating the severity of nocturnal hypoxia, such as the apnea hypopnea index, which represents the frequency of apnea and/or hypopnea episodes, total sleep time spent with SpO₂ < 90% and minimum SpO₂, but studies differ in regard to which parameter is most associated with CVD risk.^{20,21,43} While two studies concluded that minimum SpO₂ did not correlate with CVD risk and mortality in patient populations with SDB and CVD,^{44,45} other reports found that minimum SpO₂ was associated with ischemic change on ECG that represented ST-segment depression,⁴⁶ endothelial dysfunction,⁴³ obesity,⁴⁷ and nocturnal arrhythmia.⁴⁸ In these positive results, the threshold level of minimum SpO₂ that constituted a risk was $\leq 73\%$ – 83% , which was consistent with our results. Patients with a history of or risk factors for CVD may be vulnerable to myocardial injury in cases of severe desaturation, even if the desaturation is transient, because such patients have already had some asymptomatic coronary stenosis due to atherosclerosis caused by risk factors such as hypertension. Further studies will be needed to determine which index of hypoxia during nighttime is the most appropriate for discriminating high CVD risk.

4.3 | Nighttime DBP, hypoxia, and asymptomatic myocardial injury

In this study, Hs-cTnT values were significantly higher in the group of patients with the lowest tertile of nighttime DBP, and patients with minimum SpO₂ had increased likelihood of the presence of ≥ 0.014 ng/ml of Hs-cTnT compared to with those without minimum SpO₂, which suggests that the incidence of CVD may increase under the condition of overlapping lower nighttime DBP and minimum SpO₂ during nighttime. As mentioned above, each of marked nocturnal BP reduction and minimum SpO₂ during nighttime has been associated with myocardial injury, but most previous studies have investigated these associations separately. To the best of our knowledge, this is the first study to shown that marked nocturnal BP reduction and hypoxia during nighttime had additive effects on organ damage.

4.4 | BP, hypoxia, and NT-pro BNP

Our study showed that high nighttime SBP was associated with the presence of ≥ 125 pg/ml of NT-pro BNP. This finding was consistent with previous studies.^{5,6} Although it was previously reported that LV hypertrophy, mainly by the increase in LV wall stress due to hypertension, could cause an elevation of BNP plasma⁴⁹; more

recently, it was revealed that NT-pro BNP is secreted from the heart as the result of myocyte stretch, especially LV end-systolic wall stress.⁵⁰ In our present study, LVMI evaluated by echocardiography was independent of DBP and minimum SpO₂, but was associated with daytime and nighttime SBP (Table S3). On the other hand, lower daytime SBP was also associated with the presence of ≥ 125 pg/ml of NT-pro BNP. In regard to the relationship between BP and CVD risk, it has long been considered that BP reduction below a certain threshold may pose dangers, with the relation between the two parameters describing a so-called 'J-shaped curve'.⁵¹ Although our results may reflect this J-shaped curve, further studies are needed.

Although Hopkins and colleagues reported that hypoxia is related to the secretion of BNP,⁵² in our present study NT-pro BNP was not related to SpO₂ < 90% and minimum SpO₂. However, Hopkins and colleagues studied patients with cyanotic congenital heart disease, and hypoxia and NT-pro BNP were not correlated in the general population of our study.

4.5 | Limitations

There are several limitations of this study. First, we have no information about the reasons for hypoxia—for example, obstructive or central sleep apnea—in our patients. Different phenotypes of hypoxia might be associated with different impacts of desaturation during nighttime on organ damage. Second, the number of subjects in the present analysis was somewhat small. Finally, since our study was cross-sectional, further follow-up studies with larger numbers of subjects will be needed to determine whether patients with both low nighttime DBP and nocturnal hypoxia are at increased risk of CVD events.

5 | CONCLUSION

Our study demonstrated that the combination of lower nighttime DBP and minimum SpO₂ during nighttime was associated with asymptomatic myocardial injury, which was represented as higher Hs-cTnT in a clinical population with one or more CVD risks. Moreover, the patients with the coexistence of lower nighttime DBP and minimum SpO₂ were at greater risk of myocardial injury compared to those without both conditions. The findings of this study suggest that optimal nighttime BP control and improvement of hypoxia would contribute to the prevention of CVD events.

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CONFLICT OF INTEREST

K. Kario has received research grants from Omron Healthcare and A&D Co. The other authors have no conflict of interest to declare.

AUTHOR CONTRIBUTION

K Kario takes primary responsibility for this paper. K Kubota wrote the manuscript and did the statistical analysis. K Kario and Hoshide collected the patients' data. K Kario acquired research grants for the J-HOP study. K Kario and S Hoshide reviewed/edited the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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