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ORIGINAL ARTICLE

Increased nocturnal blood pressure variability is associated with renal arteriolar hyalinosis in normotensive patients with IgA nephropathy

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Abnormal blood pressure (BP) variability (BPV), occurring as beat-to-beat, 24 h, and day-to-day fluctuations, is related to target organ damage. However, the associations between abnormal BPV and renal structural changes have not been clearly investigated. We evaluated the day time and night time BP s.d. and average real variability (ARV), which reflected short-term BPV, the night time to day time (N/D) ratio of systolic BP (SBP), and the 7-day BPV, in 29 normotensive IgA nephropathy (IgAN) patients. We further compared the results with renal structural changes. The degree of arteriosclerosis was positively correlated with age, s.d. of night time SBP and the N/D ratio of SBP, and was negatively correlated with the estimated glomerular filtration rate (eGFR). The degree of arteriolar hyalinosis was positively correlated with age, night time SBP, s.d. of day time and night time SBP, day time and night time ARV, the N/D ratio of SBP and 7-day SBP, and was negatively correlated with the eGFR. A multiple linear regression analysis revealed that the level of arteriolar hyalinosis, but not arteriosclerosis, was associated with the s.d. of night time SBP ($\beta = 0.63$, $P < 0.01$) or night time ARV ($\beta = 0.61$, $P < 0.01$) after adjustment for age, sex, body mass index, the eGFR and night time SBP. Multiple linear regression analyses indicated no significant correlation between the degree of arteriolar hyalinosis and the N/D ratio of SBP or 7-day SBP s.d. or between the degree of arteriosclerosis and any of the BPV parameters. In conclusion, short-term night time BPV was found to be associated with arteriolar hyalinosis in normotensive IgAN patients.
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Keywords: arteriolar hyalinosis; IgA nephropathy; nocturnal blood pressure; short-term blood pressure variability

INTRODUCTION

Blood pressure (BP) fluctuates over a variety of durations, including beat-to-beat, 24 h and day-to-day, as well as over longer periods.[1] Several studies have indicated that both short-term[2,3] and long-term[4,5] increases in BP variability (BPV) are associated with target organ damage, which includes increases in the left ventricular mass index and the carotid-intima media thickness, fatal and non-fatal cardiovascular events, and all-cause mortality. As the kidney is extremely vulnerable to BP, it is not surprising that abnormal BPV is associated with renal damage involving microalbuminuria or macroalbuminuria[3] and a decreased glomerular filtration rate (GFR).[6] However, the associations between abnormal BPV and renal structural changes have not been clearly investigated.

Invasive intra-arterial BP monitoring is required to accurately evaluate beat-to-beat BP fluctuations. However, this approach is not practical for measuring beat-to-beat BP fluctuation in many people. Therefore, the BP s.d. data[7] or average real variability (ARV) index[8,9] that is collected by using 24 h ambulatory BP monitoring (ABPM) is used to estimate short-term BPV. An independent association between short-term BPV and a reduction in the GFR,[10] and a correlation between short-term BPV and the left ventricular mass index[11] have been demonstrated by using s.d. of systolic BP (SBP) data. The ARV index is a more precise parameter that reflects short-term BPV and is calculated with the following formula:[8,9]

$$\mathrm{ARV} = \frac{1}{N-1}\sum_{k=1}^{N-1}|\mathrm{SBP}(k+1) - \mathrm{SBP}(k)|.$$

IgA nephropathy (IgAN) is the most common type of chronic and progressive glomerular disease.[11] Hypertension-related and renal pathological changes, which include glomerular, vascular, tubular and interstitial lesions, are renal prognostic factors in IgAN patients.[12] Wu *et al.*[13] have reported that IgAN patients with intrarenal arteriosclerosis and arteriolar hyalinosis are more likely to have hypertension than patients without intrarenal arterial lesions. Although hypertension is the major risk factor for arteriosclerosis

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and arteriolar hyalinosis, ~50% of IgAN patients with normal office BP exhibit these pathological changes.[13] Furthermore, ~30% and 25% of IgAN patients who are normotensive and have dipping circadian BP patterns have intrarenal arteriosclerosis and arteriolar hyalinosis changes, respectively.[14]

As BPV increases during the early stages of chronic kidney disease, even in normotensive subjects,[3,15] we hypothesized that increased BPV during the different time intervals might be another risk factor for renal arterial damage in normotensive IgAN patients. We evaluated the s.d. of SBP and day time and night time ARV; the night time to day time (N/D) ratio of SBP; and the s.d. of the BP values measured over 7 days in 29 normotensive IgAN patients and we compared the variability of these parameters with the renal structural changes.

PATIENTS AND METHODS

Patients

This study was approved by the Ethics Committee of the Hamamatsu University School of Medicine (No. 24-171) and was conducted in accordance with the principles of the Declaration of Helsinki. All subjects provided written informed consent for participation. We recruited 29 normotensive patients who were admitted to our hospital to undergo renal biopsies and were diagnosed with IgAN between February 2012 and May 2016. The inclusion criteria for this study were patients 20–65 years of age with an office BP < 140/90 mm Hg without the use of antihypertensive agents. We excluded patients with concomitant diabetes mellitus, nephritic syndrome and severe kidney injury, which was defined as an estimated GFR (eGFR) < 45 ml min^{-1} 1.73 m^{-2}, because these factors are known to be associated with arterial lesions.[14]

Table 1 IgA nephropathy patients' clinical data

Age, years	42.7 ± 15.6
Sex, male/female	9/20
BMI, kg m^{-2}	21.2 ± 2.7
Smoking current/ex/never	2/4/23
Urinary protein, g per gCr	0.56 ± 0.41
eGFR, ml min^{-1} 1.73 m^{-2}	71.4 ± 17.7
CKD stage	1:6, 2:12, 3:11
Total cholesterol, mg dl^{-1}	193.8 ± 37.1
Low-density lipoprotein choleserol, mg dl^{-1}	107.8 ± 28.2
Uric acid, mg dl^{-1}	5.3 ± 1.3
SBP (24 h), mm Hg	112.3 ± 11.2
DBP (24 h), mm Hg	70.1 ± 8.9
HR (24 h), min^{-1}	65.6 ± 5.8
SBP (day time), mm Hg	114.3 ± 10.7
DBP (day time), mm Hg	72.6 ± 9.2
HR (day time), min^{-1}	69.0 ± 6.4
SBP (night time), mm Hg	108.5 ± 13.3
DBP (night time), mm Hg	65.4 ± 9.6
HR (night time), min^{-1}	57.6 ± 5.6
N/D ratio of SBP	0.95 ± 0.07
s.d. of SBP (24 h)	9.6 ± 2.2
s.d. of SBP (day time)	9.3 ± 2.4
ARV (day time)	8.9 ± 2.9
s.d. of SBP (night time)	8.7 ± 2.6
ARV (night time)	9.1 ± 2.8
SBP (7 days), mm Hg	111.2 ± 8.7
DBP (7 days), mm Hg	67.8 ± 8.0
s.d. of SBP (7 days)	7.6 ± 2.4

Abbreviations: ARV, average real variability; BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HR, heart rate; N/D, night time to day time; SBP, systolic blood pressure.

Study protocol

ABPM monitoring was conducted at 30 min intervals during the day and night with an automatic device (TM-2431; A and D, Tokyo, Japan). The day time and night time periods were defined according to the patients' behavior records. Daytime, which was defined as the period from 0600 to 2100 h, and night time, which was defined as the period from 2100 to 0600 h, urine collections were conducted as previously described.[16] Blood samples were drawn at 0600 h at the end of the ABPM. The mean BP values, s.d. and ARV were calculated for the day time and night time BP. The BP circadian rhythms were classified as extreme dipper, dipper, nondipper and riser when the N/D ratios of the SBP were < 0.80, 0.80– < 0.90, 0.90–1.0 and > 1.0, respectively.

The SBP and the diastolic BP were measured every morning. We measured the BP for 8 days but excluded the data from the next day, which was when the renal biopsy was performed, and the mean BP and s.d. for the other 7 days were calculated.

Clinical data

The patients' clinical data, including age, sex, body mass index and history of smoking, were collected at the time of admission. Serum creatinine (Cr), uric acid, total cholesterol and low-density lipoprotein cholesterol concentrations, as well as urinary Cr and protein concentrations, were measured in the clinical laboratory at the Hamamatsu University School of Medicine.

Histopathological data

The levels of arteriosclerosis (0: normal; 1: intimal thickness less than media thickness; and 2: intimal thickness more than media thickness) and arteriolar hyalinosis (the proportion of affected arterioles, 0: absent; 1: 1–25%; 2: 26–50%; and 3: 51–100%) in the intrarenal artery were scored in accordance with the Oxford classification of IgAN using sections stained by periodic acid-Schiff and Elastica van Gieson stains, respectively.[17] The percentages of tubulointerstitial damage and global glomerulosclerosis were evaluated from sections stained with Masson's trichrome and periodic acid-Schiff, respectively.

Statistical analyses

The results are expressed as mean ± s.d. The significance of the differences between the patients with or without arteriosclerosis and arteriolar hyalinosis in relation to their clinical data was determined using Student's *t*-test for unpaired samples. The correlations between the renal structural changes and the clinical parameters were evaluated using Pearson's product–moment correlation test. Multiple linear regression analyses were conducted to evaluate the relationships between the renal structural changes, namely arteriosclerosis and arteriolar hyalinosis, and the different BPV parameters. Sex and body mass index were selected as variables, because these parameters are commonly used in multiple linear regression analyses. In addition, age, the eGFR and SBP were also adjusted, because they are associated with arterial lesions. We selected SBP parameters at the same time point as BPV parameters. We considered a value of $P < 0.05$ to be statistically significant. The statistical analyses were performed using the IBMSPSS software, version 20 (IBM Corporation, Armonk, NY, USA).

RESULTS

Patient characteristics

Renal biopsy was performed in a total of 201 patients at our hospital during the study duration. Sixty-nine of the patients were diagnosed as IgAN and 29 were enrolled in this study (Supplementary Figure 1). The baseline characteristics are presented in Table 1. The classification of the BP circadian rhythms showed that among the participants, 6 were dippers, 18 were nondippers and 5 were risers. None of the participants exhibited the extreme dipper BP pattern. Among the 29 patients, 4 took lipid-lowering agents and none received uric acid-lowering agents. Twenty-three patients consumed a low-salt diet containing 6 g per day of sodium chloride and the others consumed a standard diet (10 g per day of sodium chloride).

Table 2 Relationships between the clinical data and the pathological parameters in IgA nephropathy patients

	Arteriosclerosis		*Arteriolar hyalinosis*		*Global sclerosis*		*Tubulointerstitial damage*	
	r	P-*value*	r	P-*value*	r	P-*value*	r	P-*value*
Age, years	0.64	<0.01	0.46	0.01	0.34	0.07	0.44	0.02
Sex	−0.14	0.48	0.12	0.52	−0.19	0.32	−0.09	0.63
BMI, kg m^{-2}	0.13	0.50	0.22	0.26	0.02	0.92	0.06	0.78
Urinary protein (day time), g per gCr	0.22	0.24	0.04	0.85	0.08	0.68	0.14	0.46
Urinary protein (night time), g per gCr	0.28	0.14	0.15	0.44	0.08	0.68	0.12	0.52
eGFR, ml min^{-1} 1.73 m^{-2}	−0.60	<0.01	−0.45	0.01	−0.47	0.01	−0.47	0.01
SBP (24 h), mm Hg	0.15	0.44	0.34	0.23	−0.01	0.96	0.06	0.77
DBP (24 h), mm Hg	0.12	0.55	0.07	0.23	0.04	0.82	0.06	0.77
HR (24 h), min^{-1}	−0.06	0.77	−0.19	0.32	0.07	0.70	−0.03	0.86
SBP (day time), mm Hg	0.02	0.90	0.26	0.18	−0.09	0.64	−0.03	0.89
DBP (day time), mm Hg	0.01	0.96	0.16	0.42	−0.01	0.96	−0.02	0.94
HR (day time), min^{-1}	−0.06	0.77	−0.18	0.36	0.11	0.59	−0.27	0.89
SBP (night time), mm Hg	0.33	0.08	0.45	0.02	0.14	0.48	0.20	0.30
DBP (night time), mm Hg	0.28	0.14	0.33	0.08	0.12	0.55	0.14	0.47
HR (night time), min^{-1}	−0.078	0.69	−0.06	0.76	−0.05	0.98	0.10	0.60
N/D ratio of SBP	0.54	<0.01	0.40	0.03	0.37	0.048	0.40	0.03
s.d. of SBP (day time)	0.31	0.10	0.44	0.02	−0.11	0.59	−0.07	0.70
ARV (day time)	0.36	0.052	0.53	<0.01	0.03	0.90	0.04	0.86
s.d. of SBP (night time)	0.38	0.04	0.56	<0.01	−0.06	0.74	0.03	0.89
ARV (night time)	0.28	0.15	0.69	<0.01	−0.09	0.64	0.40	0.03
SBP (7 days), mm Hg	0.10	0.59	0.44	0.02	−0.03	0.89	0.09	0.64
DBP (7 days), mm Hg	0.14	0.46	0.36	0.06	0.18	0.36	0.08	0.67
s.d. of SBP (7 days), mm Hg	-0.04	0.86	0.20	0.30	−0.22	0.24	<0.01	0.99
s.d. of DBP (7 days), mm Hg	0.14	0.47	0.22	0.25	−0.22	0.25	0.05	0.81

Abbreviations: ARV, average real variability; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HR, heart rate; N/D, night time to day time; SBP, systolic blood pressure.

Relationships between the clinical data and the pathological changes

We investigated the correlations between the clinical parameters and the pathological changes. Intrarenal arteriosclerosis was positively correlated with age, the N/D ratio of s.d. of night time SBP, and it was negatively correlated with the eGFR. Arteriolar hyalinosis was positively correlated with age, the N/D ratio of SBP, the night time SBP, the s.d. of the day time and night time SBP, the day time and night time ARV and the 7-day SBP, and it was negatively correlated with the eGFR. The percentages of the glomerulosclerosis and the tubulointerstitial damage were positively correlated with age and the N/D ratio of SBP and were negatively correlated with the eGFR (Table 2). There were no significant correlations between renal pathological changes and the other risk factors, such as a history of smoking, the lipid profile and the serum uric acid concentration (Supplementary Table 1).

Clinical characteristics in the presence and absence of arteriosclerosis and arteriolar hyalinosis in the kidney

Given that the BPV parameters appeared to be related to arteriosclerosis and arteriolar hyalinosis lesions, we evaluated the clinical data in the presence and absence of these lesions. The IgAN patients with arteriosclerosis were significantly older, had lower eGFRs, had higher N/D ratios of SBP and tended to have higher night time BP, as compared with the IgAN patients who did not have arteriosclerosis. There were no significant differences between the IgAN patients who had and did not have arteriosclerosis in relation to day time BP, the s.d. of the day time and night time SBP, day time and night time ARV and the 7-day BP and s.d. (Table 3).

The IgAN patients with arteriolar hyalinosis had significantly higher N/D ratios of SBP, night time SBP, s.d. of the night time SBP and night time ARV, as well as lower eGFRs, as compared with patients who did not have arteriolar hyalinosis. The IgAN patients with arteriolar hyalinosis tended to be older and tended to have higher s.d. of the day time SBP and 7-day diastolic BP, as compared with patients who did not have arteriolar hyalinosis (Table 3).

Multiple linear regression analyses of the renal structural changes and the clinical parameters

We performed multiple linear regression analyses to evaluate the relationships between the renal structural changes, namely arteriosclerosis and arteriolar hyalinosis, and the clinical parameters. Multiple linear regression analyses showed that arteriolar hyalinosis was associated with the s.d. of night time SBP and night time ARV after adjustment for age, sex, body mass index, the eGFR and night time SBP. The multiple linear regression analyses also showed that the other BPV parameters, such as the s.d. of day time SBP, day time ARV, the N/D ratio of SBP and the s.d. of the 7-day BP, were not correlated with arteriolar hyalinosis after adjustment for age, sex, body mass index, the eGFR, day time SBP, night time SBP and the 7-day SBP (Table 4). A multiple linear regression analysis showed that the s.d. of day time and night time SBP, the day time and night time ARV, the N/D ratio of SBP and the s.d. of the 7-day SBP were not associated with arteriosclerosis (data not shown).

Table 3 Clinical data from IgA nephropathy patients with or without renal arteriosclerosis and arteriolar hyalinosis

	Arteriosclerosis			*Arteriolar hyalinosis*		
	Absent	*Present*	P-*value*	*Absent*	*Present*	P-*value*
Number (%)	17 (58.6)	12 (41.4)		12 (41.4)	17 (58.6)	
Age, years	34.8±11.0	53.7±14.9	<0.01	36.5±13.9	47.0±15.7	0.074
Sex, male/female	11-Jun	9-Mar	0.57	8-Apr	12-May	0.83
BMI, kg m^{-2}	21.3±2.2	21.1±3.4	0.89	20.9±2.4	21.5±3.0	0.54
Urinary protein (day time), g per gCr	0.46±0.27	0.65±0.48	0.18	0.45±0.25	0.65±0.48	0.19
Urinary protein (night time), g per gCr	0.31±0.17	0.53±0.45	0.12	0.28±0.18	0.48±0.39	0.11
eGFR, ml min^{-1} 1.73 m^{-2}	79.8±16.6	59.4±11.3	<0.01	79.1±20.4	66.0±13.6	0.047
SBP (24 h), mm Hg	110.9±11.6	114.3±10.8	0.44	108.7±6.4	114.9±13.2	0.14
DBP (24 h), mm Hg	68.8±9.8	71.9±7.5	0.37	68.4±5.7	71.3±10.6	0.4
HR(24 h), min^{-1}	65.4±6.1	65.8±5.0	0.88	67.0±6.1	64.5±5.1	0.25
SBP (day time), mm Hg	114.2±11.1	114.6±10.7	0.93	111.8±7.0	116.2±12.6	0.28
DBP (day time), mm Hg	72.1±10.1	73.3±8.0	0.75	71.4±6.1	73.4±10.9	0.57
HR (day time), min^{-1}	68.9±6.9	69.2±4.9	0.92	70.5±7.2	68.0±5.1	0.28
SBP (night time), mm Hg	104.7±13.8	113.8±10.9	0.069	102.8±6.6	112.5±15.3	0.047
DBP (night time), mm Hg	62.7±10.1	69.3±7.7	0.069	62.6±7.0	67.4±10.8	0.19
HR (night time), min^{-1}	57.6±4.8	58.3±6.4	0.75	58.6±5.2	57.5±5.7	0.6
N/D ratio of SBP	0.92±0.06	0.99±0.04	<0.01	0.92±0.05	0.97±0.07	0.046
s.d. of SBP (day time)	8.9±2.0	10.1±2.8	0.19	8.3±1.7	10.1±2.6	0.051
ARV (day time)	8.6±1.9	9.3±3.9	0.53	8.0±1.6	9.5±3.4	0.11
s.d. of SBP (night time)	8.1±2.5	9.6±2.6	0.11	7.4±1.9	9.7±2.7	0.02
ARV (night time)	8.8±2.2	9.6±3.5	0.45	7.9±1.5	10.0±3.1	0.03
SBP (7 days), mm Hg	111.24±9.2	111.2±8.3	0.99	108.1±5.7	113.5±9.9	0.1
DBP (7 days), mm Hg	66.7±9.9	69.3±4.0	0.4	64.6±7.3	70.0±7.9	0.07
s.d. of SBP (7 days), mm Hg	9.0±2.2	8.8±3.2	0.84	9.0±2.2	8.9±3.0	0.95
s.d. of DBP (7 days), mm Hg	7.2±2.2	8.1±2.6	0.34	7.2±2.4	7.9±2.5	0.46

Abbreviations: ARV, average real variability; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HR, heart rate; N/D, night time to day time; SBP, systolic blood pressure.

Table 4 Multiple linear regression analyses of the associations between arteriolar hyalinosis and the clinical parameters in IgA nephropathy patients

	Model 1		*Model 2*		*Model 3*		*Model 4*		*Model 5*		*Model 6*	
	r=0.63	*p*=0.06	*r*=0.64	*p*=0.06	*r*=0.79	*p*<0.01	*r*=0.78	*p*<0.01	*r*=0.59	*p*=0.11	*r*=0.62	*p*=0.07
	β	P-*value*	β	P-*value*	β	P-*value*	β	P-*value*	β	P-*value*	β	P-*value*
Age	0.13	0.59	0.23	0.32	−0.17	0.41	0.05	0.8	0.19	0.36	0.02	0.95
Sex	0.16	0.39	0.1	0.58	0.01	0.92	−0.09	0.58	0.16	0.46	0.11	0.56
BMI	0.18	0.32	0.07	0.73	0.31	0.04	−0.03	0.83	0.16	0.42	0.15	0.4
eGFR	−0.3	0.18	−0.16	0.46	−0.44	0.02	−0.15	0.42	−0.21	0.4	−0.38	0.12
SBP (daytime)	0.005	0.98	0.03	0.86								
SD of SBP (daytime)	0.33	0.091										
ARV (daytime)			0.36	0.08								
SBP (nighttime)					0.19	0.24	0.28	0.1	0.17	0.5		
SD of SBP (nighttime)					0.63	<0.01						
ARV (nighttime)							0.61	<0.01				
N/D ratio of SBP									0.12	0.61		
SBP (7-days)											0.3	0.15
SD of SBP(7-days)											0.14	0.47

Abbreviations: BMI: body mass index; eGFR: estimated glomerular filtration rate; SBP: systolic blood pressure; SD: standard deviation; ARV: average real variability; N/D: nighttime to daytime

DISCUSSION

Although the associations between target organ damage and the different types of BPV are well established,[1] the associations between abnormal BPV and renal structural changes have not been clearly defined until now. In the present study, we recruited 29 normotensive IgAN patients and the results demonstrated that the degree of arteriolar hyalinosis, but not arteriosclerosis, was associated with the s.d. of night time SBP and night time ARV in the multiple linear

regression analysis. Even though the mean BP in the IgAN patients was low, only 21% of the patients had normal BP circadian rhythms, and 62% and 17% of the patients had nondipper and riser patterns, respectively.

Haruhara *et al.*[18] have investigated the correlation between ABPM parameters and renal histological changes in 138 patients with various types of kidney diseases and have demonstrated that day time and night time BP values are associated with tubulointerstitial damage but not arteriosclerosis or arteriolar hyalinosis. However, they did not investigate the short-term BPV. In addition, the N/D ratio of SBP was not found to be correlated with renal arterial lesions. However, 48% of the study patients received antihypertensive agents, which influenced not only BP but also the BPV. Furthermore, patients with diabetes mellitus, severe renal failure and various types of kidney disease were included, thus potentially influencing arterial lesions.[19,20] The discrepancy between their results and our results may be explained by the different patient characteristics.

The pathogenic mechanisms underlying arteriosclerosis and arteriolar hyalinosis are not fully understood.[21] The results from a population-based autopsy study have shown that the prevalence of arteriosclerosis and arteriolar hyalinosis increase similarly with increasing age and BP.[22] Wu *et al.*[13] have reported that the prevalence of arterial lesions is 54.6% in IgAN patients, and 26.6% and 47.1% in non-IgAN and membranous nephropathy patients, respectively, even though the IgAN patients were younger when the renal biopsies were conducted. Furthermore, the prevalence of arteriolar hyalinosis is dramatically higher in IgAN patients (43.7%) compared with patients with other renal diseases, namely non-IgAN patients (16.8%) and membranous nephropathy patients (21.5%).[13] Therefore, it is possible that the pathogenic mechanisms in IgAN patients may influence arteriolar hyalinosis. The reasons underlying the presence of an association between short-term BPV and arteriolar hyalinosis, but not between short-term BPV and atherosclerosis, remain unclear but may potentially explain the mechanisms aside from BP that affect arteriolar hyalinosis and arteriosclerosis.

We determined a correlation between abnormal BPV and arterial hyalinosis in normotensive IgAN patients. However, little is known about the associations between abnormal BPV and the renal pathological changes in hypertensive patients. Nagasawa *et al.*[23] have demonstrated that urinary albumin excretion is associated with injury to the glomeruli and with pressure-associated injuries to the preglomerular vessels in spontaneously hypertensive stroke-prone rats. Furthermore, as the kidney has an autoregulatory vasoconstrictor response, an increase in the systemic BP does not directly affect intraglomerular pressure.[24] It is possible that pressure-associated arteriolar injury has already occurred before glomerular basement membrane injury is detected as albuminuria or proteinuria. In fact, Zamami *et al.*[25] have reported that dysregulated afferent arteriolar resistance via arteriolar sclerosis may affect hypertensive renal damage. The tonus of efferent arterioles is known to be regulated by several factors, such as the intrarenal renin-angiotensin system,[26] decreased adenosine A2a receptor-mediated vasodilatation[27] and increased asymmetrical dimethylarginine.[28] However, the associations among ABPM, hyalinosis and failed autoregulation of efferent arterioles is not clear. Further studies are needed to clarify these relationships.

In this study, the multiple regression analysis showed that short-term night time, but not short-term day time, BPV was associated with arteriolar hyalinosis. Several studies have demonstrated that, compared with day time BP, nocturnal BP is superior at predicting the incidence of cardiovascular events and all-cause mortality.[29,30] Physical activity and environmental changes that influence short-term BPV are less frequent at night than during the day. As short-term night time BPV reflects endogenous factors rather than external factors, it is reasonable to assume that short-term night time BPV is more useful than short-term day time BPV for predicting renal structural changes.

Central sympathetic nervous system activation is a consequence of renal disease[31,32] and is an important mechanism underlying the augmentation of short-term BPV.[1] In general, arterial lesions are increased by shear stress.[33] However, other factors, including smoking, obesity, inflammation, reactive oxygen species and renin-angiotensin system, also influence arterial lesions.[19,20,34] In particular, it is well known that both intrarenal renin-angiotensin system and reactive oxygen species are activated in IgAN patients and IgAN mouse models.[35,36] These morbidities may cause not only the progression of arterial hyalinosis but also incremental changes in short-term BPV via an activated central sympathetic nervous system. In the near future, we will design a study to clarify the relationships among arterial hyalinosis, short-term BPV and the central sympathetic nervous system.

A history of smoking, the lipid profile and the serum uric acid concentration are important risk factors for atherosclerosis. However, in the present study, there were only 2 and 4 patients who were current smokers and ex-smokers, respectively. Furthermore, the levels of average total cholesterol and uric acid were within normal limits (total cholesterol 193.8 ± 37.1 mg dl^{-1} and uric acid 5.3 ± 1.3 mg dl^{-1}). These homogeneous and favorable patient characteristics may explain why these risk factors did not correlate with the arterial lesions.

There are some limitations to the present study. First, the study's sample size was relatively small. Lin *et al.*[14] have conducted logistic regression analyses of the abnormal BP circadian rhythms in 330 normotensive IgAN patients and have demonstrated that a nondipping BP pattern is associated with the eGFR, severe renal interstitial fibrosis, and arteriosclerosis in the renal arcuate arteries. Therefore, the present study's inability to demonstrate an association between the N/D ratio of BP and renal structural damage in this study might be a consequence of the study being underpowered. However, an association between short-term night time BPV and arteriolar hyalinosis was demonstrated in normotensive IgAN patients in this study despite the small sample size. Second, the ABPM was performed and the BP was measured while the participants were hospitalized. An increase in day-to-day BPV is associated with the severity of the left ventricular mass index, increased carotid intima-media thickness and urinary albumin excretion.[37] However, in this study we did not find any correlation between day-to-day BPV and renal pathological damage. Although little is known about the factors that influence day-to-day BPV, behavioral changes are considered the most likely influencing factors,[38] thus potentially explaining the lack of an association between day-to-day BPV and structural renal arteriolar damage in this study.

In conclusion, short-term night time BPV was found to be associated with arteriolar hyalinosis in normotensive IgAN patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on Hypertension Research website (http://www.nature.com/hr)