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(Citation)
Kidney & Blood Pressure Research,41(4):374-383

(Issue Date)
2016-06-20

(Resource Type)
journal article

(Version)
Version of Record

(URL)
https://hdl.handle.net/20.500.14094/90003551

Kidney & Blood Pressure Research

Kidney Blood Press Res 2016;41:374-383
DOI: 10.1159/000443440
Published online: June 20, 2016
Accepted: April 26, 2016

Original Paper

Relationship Between Type of Hypertension and Renal Arteriolosclerosis in Chronic Glomerular Disease

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Key Words
Ambulatory blood pressure • Circadian rhythm of blood pressure • Arteriolosclerosis • Masked hypertension • Renal arteriolosclerosis • Glomerular disease

Abstract
Background/Aims: Hypertension (HT) is a common complication in patients with chronic kidney disease (CKD). However, the relationship between circadian rhythm disorder of blood pressure (BP) and intra-renal damage remains unclear. ***Methods:*** Ninety patients with chronic glomerular disease (CGD) were included in the present study. On the basis of the clinic BP (CBP) and 24 h-ambulatory BP (ABP) measurements, the patients were divided into the following groups; normotension (NT), white coat HT (WHT), masked HT (MHT), and sustained HT (SHT). For renal histopathological assessment, we evaluated each biopsy specimen for sclerotic glomeruli (SG), interstitial fibrosis (IF), intimal thickening of intra-lobular arteries (ILA), and arteriolar hyalinosis (AH). ***Results:*** The prevalence of NT, WHT, MHT and SHT was 60.0%, 3.3%, 23.3%, and 13.4%, respectively. Compared with circadian BP pattern, all-day HT was most prevalent in the SHT group, whereas nighttime HT was most prevalent in the MHT group. The results of histological analysis showed that the SHT group had more severe SG and IF and the MHT group had more severe IF compared to the NT group. As for renal arteriolosclerosis, the MHT and SHT groups had more severe AH compared with the NT group, whereas ILA was comparable among all four groups. Furthermore, multivariate analysis revealed that ILA was significantly correlated only with age, whereas AH was significantly correlated with age and HT based on ABP, but not HT based on CBP. ***Conclusions:*** Our findings suggest that renal AH was severe not only in the SHT group, but also in the MHT group. Careful ABP monitoring should be recommended in patients with CGD.

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Kidney & Blood Pressure Research

Kidney Blood Press Res 2016;41:374-383
DOI: 10.1159/000443440
Published online: June 20, 2016

Introduction

Hypertension (HT) is both a major cause and complication of chronic kidney disease (CKD) [1-4], with a reported prevalence of more than 80% of patients in CKD [5]. Furthermore, HT is the traditional risk factor for cardiovascular events and could lead to a vicious cycle of cardio-renal disease in patients with CKD. Therefore, the importance of blood pressure (BP) control in slowing the progression of renal disease and cardiovascular disease (CVD) is well recognized.

Clinic blood pressure (CBP) has been commonly used for the assessment of BP in the clinical setting. However, there is a possibility to underestimate the true BP because of its circadian rhythm disorder. On the other hand, ambulatory BP (ABP) monitoring could provide more precise BP information and it has been reported to have better clinical correlations with various damages to target organs, including the kidney [6, 7]. Recently, there was accumulating evidence that similar to sustained HT, rhythm disorder of BP, such as situational HT and nocturnal HT, was an independent risk factor for developing CKD as well as CVD [8-11]. It was reported that the prevalence of masked HT and nocturnal HT was relatively high in a CKD population [12, 13]. However, the relationship between ABP and renal histological damage remains unclear. Therefore, we investigated their relationship in patients with chronic glomerular disease (CGD) who underwent renal biopsy.

Materials and Methods

Study population and design

Ninety consecutive patients who underwent renal biopsy for the diagnosis of GD between April 2010 and March 2015 at Kobe University Hospital and Akashi Medical Center were included in the present study. All the study patients had persistent urinalysis abnormalities for at least 3 months. Patients with antihypertensive therapy, diabetes mellitus, malignancy, nephrotic syndrome, vasculitis, and acute kidney injury as well as those with insufficient data were excluded from the present study. The institutional review boards of Kobe University Hospital and Akashi Medical Center approved the present study.

Blood pressure measurements

CBP was measured with the use of a mercury sphygmomanometer, in a sitting position after five minutes of rest, and with the patient's arm kept at the heart level. The average of three-visit CBP measurements was calculated. ABP monitoring was performed using TM 2431 (A & D company, Ltd. Tokyo, Japan) for 24 h; BP was automatically measured every 30 min during daytime and every 1 h during nighttime. After detaching ABP monitoring, we excluded the ABP data which did not satisfy the following condition according to the guidelines from the Japanese Circulation Society (JCS) [14]; 1) 70≤ systolic BP (mmHg)≤ 250, 2) 30≤ diastolic BP (mmHg)≤ 130, 3) 20≤ Pulse pressure (PP; (mmHg))≤ 16, 4) PP (mmHg) > 0.41×diastolic BP (60 to 150 mmHg) -17mmHg. All patients kept a diary, on which the sleep and awake times were based. We confirmed that at least 20 valid awake and 7 valid asleep measurements were recorded in each study patient according to the European Society of Hypertension practice guidelines for ABPM [15]. For the assessment of circadian BP rhythm, sleep ABP/awake ABP ratio was calculated. According to sleep systolic ABP/awake systolic ABP ratio, patients were classified as "extreme-dipper" (< 0.8), "dipper" (0.8–0.9), "non-dipper" (0.9–1.0), or "riser" (>1.0).

Definitions of hypertension

Hypertension was defined according to the guidelines of the Japanese Society of Hypertension (JSH) [16] as follows: (1) CBP hypertension (CBPHT) as an average CBP of ≥140/90 mmHg and (2) ABP hypertension (ABPHT) as an average 24-h ABP of ≥130/80 mmHg, awake ABP of ≥135/85 mmHg, and sleep ABP of ≥120/70 mmHg. Normotension (NT) was diagnosed when CBP and ABP were within the normotensive range. A diagnosis of MHT was made if CBP was within the normotensive range and ABP was within the hypertensive range. White coat hypertension (WHT) was diagnosed when CBP was within

the hypertensive range and ABP was within the normotensive range. Sustained hypertension (SHT) was diagnosed when CBP and 24-h ABP were within the hypertensive range. Furthermore, nighttime HT was diagnosed when awake ABP was within the normotensive range and sleep ABP was within the hypertensive range; daytime HT was diagnosed when sleep ABP was within the normotensive range and awake ABP was within the hypertensive range; and all-day HT was diagnosed when both sleep ABP and awake ABP were within the hypertensive range.

Histological analysis of renal tissue damage

Renal biopsy samples were taken from the lower pole of the kidney under ultrasonography guidance. Specimens were immediately fixed in formaldehyde for light microscopy and in Karnovsky's solution or 2.5% glutaraldehyde for electron microscopy. For immunostaining, tissues were immediately snap frozen. A pathologic diagnosis of GD for each renal biopsy specimen was made after light microscopy, immunofluorescence, and electron microscopy. For the assessment of renal tissue damage, three observers evaluated for glomerular, interstitial, and intra-renal vascular abnormalities in each biopsy specimen. Sclerotic glomeruli (SG) and interstitial fibrosis (IF) were described as [100 × (the number of sclerotic glomeruli/the total number of glomeruli)] and [100 × (the area of interstitial fibrosis/all the interstitial area)], respectively. For intra-renal vascular lesions, the intimal thickening of intra-lobular arteries (ILA) and arteriolar hyalinosis (AH) were classified into four grades (none = 0, mild = 1, moderate = 2, and severe = 3) [17].

Statistical analysis

All values are expressed as mean ± standard deviation (SD). Statistical analyses were performed using SPSS II for Windows, version 11.01J (Chicago, IL, USA). Comparisons among groups were analyzed by the X^2 test for categorical variables and by one-way analysis for variance for continuous variables, followed by the Scheffe's *post-hoc* test. Univariate and multivariate regression analyses were performed to assess the relationship between renal histopathological findings and clinical characteristics. Univariate analysis was performed by Pearson correlation analysis for parametric parameters and Spearman correlation analysis for non-parametric parameters. We performed multiple linear regression analysis for multivariate analysis. $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

The histological diagnosis of each patient was IgA nephropathy (n= 62 (69%)), focal segmental global sclerosis (n= 6 (7%)), thin basement membrane disease (n= 6 (7%)), membranous nephropathy (n=4 (4%)), and the others (n=12 (13%)).The prevalence of NT, WHT, MHT, and SHT was 60.0%, 3.3%, 23.3%, and 13.4%, respectively (Figure 1). Patient characteristics are presented in Table 1. Age, body mass index (BMI), and serum creatinine levels were significantly higher in the SHT group than in the NT group. Total cholesterol was significantly higher in the MHT group than in the NT group. The proportion of male sex was higher in the MHT and SHT groups than in the NT and WHT groups. There was no significant difference among the NT, WHT, and MHT groups in terms of the other clinical characteristics.

Clinic and ambulatory blood pressure

Table 2 shows the results of CBP and ABP monitoring. CBP was significantly higher in the WHT and SHT group than in the NT group. In the MHT group, systolic CBP was significantly higher than in the NT group; however, the value of BP was within normotensive range. In the ABP analysis, awake ABP, sleep ABP, and average 24-h ABP were significantly higher in the MHT group than in the NT group. Regarding circadian BP pattern, "riser" tended to be highly prevalent in the MHT and SHT groups than in the NT and WHT groups (NT: 5%, WHT: 0%, MHT: 29%, and SHT: 25%). Furthermore, nighttime HT was most prevalent in the MHT group (48%), whereas all-day HT was most prevalent in the SHT group (75%).

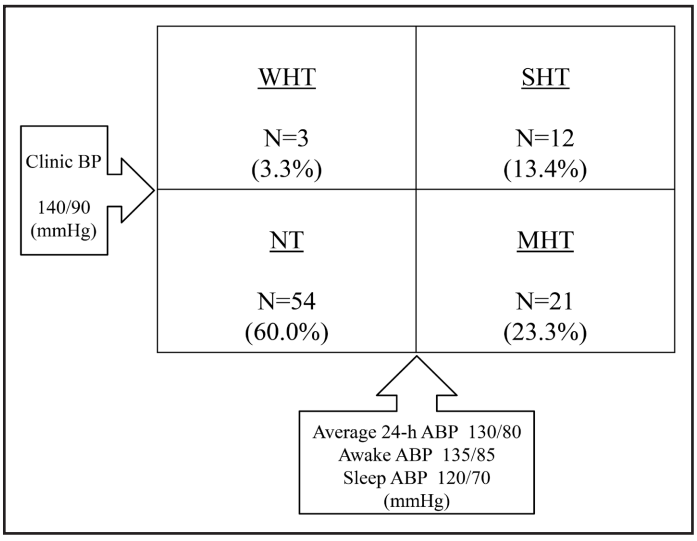

Fig. 1. Classification of patients according to CBP and ABP

Table 1. Clinical data in NT, WHT, MHT and HT groups

	NT (n= 54)	WHT (n= 3)	MHT (n = 21)	SHT (n = 12)	*p*
Age (y.o.)	33 ± 12	47 ± 6	40 ± 17	43 ± 13 *	< 0.05
Sex (male, n (%))	17 (31)	0 (0)	14 (67)	8 (67)	< 0.05
BMI (kg/m^2)	20.6 ± 2.9	23.0 ± 3.5	21.6 ± 2.4	23.2 ± 3.8 *	< 0.05
Smoking (n (%))	13 (24)	0 (0)	10 (48)	5 (42)	0.12
Dyslipidemia (n (%))	7 (13)	1 (33)	4 (19)	3 (25)	0.61
Serum albumin (g/dl)	4.1 ± 0.5	4.1 ± 0.4	3.8 ± 0.6	3.9 ± 0.6	0.29
Serum creatinine (g/dl)	0.7 ± 0.1	0.8 ± 0.1	0.9 ± 0.3	1.2 ± 1.4 *	< 0.05
eGFR (ml/min/1.73m^2)	88.2 ± 19.7	62.1 ± 10.8	77.9 ± 18.1	69.2 ± 22.9 *	< 0.05
CRP (mg/dl)	0.1 ± 0.1	0.2 ± 0.2	0.1 ± 0.1	0.1 ± 0.1	0.07
T-chol (mg/dl)	197.1 ± 35.4	212.0 ± 33.4	225.6 ± 40.9 *	212.0 ± 42.8	< 0.05
HDL (mg/dl)	72.4 ± 23.2	61.0 ± 18.2	67.2 ± 13.5	66.9 ± 18.9	0.59
Triglyceride (mg/dl)	101.8 ± 66.2	110.7 ± 90.0	133.5 ± 93.0	124.4 ± 83.9	0.40
Urinary protein (g/gCre)	0.9 ± 0.7	0.5 ± 0.3	1.5 ± 1.5	1.7 ± 1.9	0.05

BMI: body mass index, eGFR: estimated glomerular filtration rate, CRP: C reactive protein , T-chol: total cholesterol, HDL: high density lipoprotein, * p< 0.05 versus NT group

Table 2. Ambulatory blood pressure data in NT, WHT, MHT and SHT groups

		NT (n= 54)	WHT (n= 3)	MHT (n = 21)	SHT (n = 12)	*p*
CBP (mmHg)	systolic	110 ± 11	143 ± 2 *	120 ± 10 *+	146 ± 10 *++	< 0.01
	diastolic	64 ± 9	84 ± 9 *	70 ± 10	92 ± 9 *++	< 0.01
Awake ABP (mmHg)	systolic	113 ± 7	114 ± 1	133 ± 10 *+	137 ± 15 *+	< 0.01
	diastolic	68 ± 5	72 ± 3	78 ± 8 *+	83 ± 8 *+	< 0.01
Sleep ABP (mmHg)	systolic	104 ± 7	101 ± 5	125 ± 9 *+	129 ± 17 *+	< 0.01
	diastolic	61 ± 4	74 ± 10	74 ± 10 *	79 ± 9 *+	< 0.01
24 h ABP (mmHg)	systolic	111 ± 7	111 ± 2	131 ± 9 *+	135 ± 15 *+	< 0.01
	diastolic	67 ± 4	70 ± 3	77 ± 7 *	82 ± 8 *+	< 0.01
Sleep/awake BP ratio	systolic	0.91 ± 0.05	0.89 ± 0.03	0.95 ± 0.07	0.94 ± 0.06	0.07
	diastolic	0.90 ± 0.06	0.86 ± 0.02	0.94 ± 0.11	0.96 ± 0.06 *	< 0.01
Type of nocturnal BP fall (n (%))	dipper	22 (41)	2 (67)	6 (28)	3 (25)	0.12
	non-dipper	29 (54)	1 (33)	9 (43)	6 (50)	
	riser	3 (5)	0 (0)	6 (29)	3 (25)	
	extreme-dipper	0 (0)	0 (0)	0 (0)	0 (0)	
Type of HT (n (%))	daytime HT	-	-	2 (9)	0 (0)	< 0.01
	nighttime HT	-	-	10 (48)	3 (25)	
	all-day HT	-	-	9 (43)	9 (75)	

CBP : clinic blood pressure, ABP: ambulatory blood pressure, BP: blood pressure, HT: hypertension * p< 0.05 versus NT group, + p< 0.05 versus WHT group, ++ p< 0.05 versus MHT group

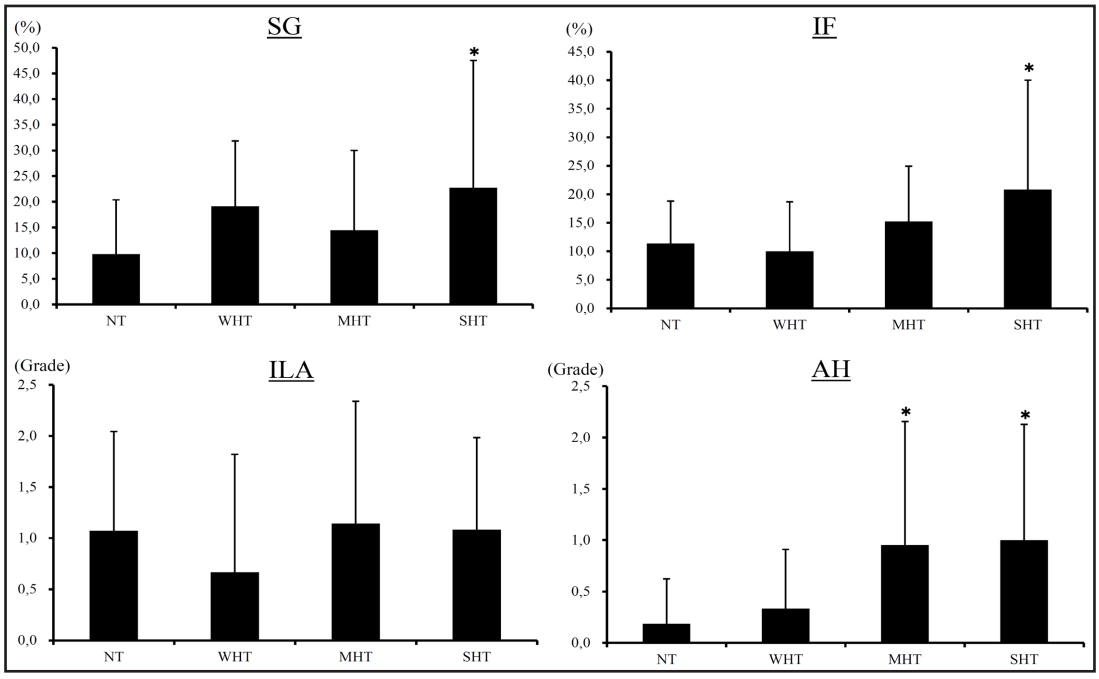

Fig. 2. Comparison of pathological findings between NT, WHT, MHT and SHT groups. SG: sclerotic glomeruli, IF: interstitial fibrosis, ILA: intimal thickening of intra-lobular arteries, AH: arteriolar hyalinosis. * $p < 0.05$ versus NT group.

Comparison of histological analysis for renal tissue damage among the NT, WHT, MHT, and SHT groups

Figure 2 shows comparison of histopathological analysis for renal tissue damage among all four groups. The percentages of SG and IF were significantly greater in the SHT group than in the NT group. The MHT group also had more progressed IF compared with the NT and WHT groups, however, this was not statistically significant (NT: 11.4 ± 7.4%, WHT: 10.0 ± 8.7%, MHT 15.2 ± 9.7%). As for intra-renal vascular lesions, the grade of AH was significantly greater in the SHT group than in the NT group (1.0 ± 1.1 vs. 0.2 ± 0.4, respectively; $p < 0.05$). Furthermore, the MHT group also had significantly more severe AH compared with the NT group (1.0 ± 1.2 vs. 0.2 ± 0.4, respectively; $p < 0.05$). ILA was comparable among all four groups.

Relationship between renal histological analysis and clinical characteristics

Tables 3 and 4 show the relationship between renal histological analysis and clinical characteristics. SG was significantly correlated with smoking ($r = 0.221$, $p < 0.05$), estimated glomerular filtration rate (eGFR) ($r = -0.542$, $p < 0.01$), urinary protein ($r = 0.239$, $p < 0.05$), ABPHT ($r = 0.234$, $p < 0.05$), CBPHT ($r = 0.266$, $p < 0.05$), NT ($r = -0.258$, $p < 0.05$), and SHT ($r = 0.260$, $p < 0.05$). IF was significantly correlated with smoking ($r = 0.234$, $p < 0.05$), eGFR ($r = -0.554$, $p < 0.01$), urinary protein ($r = 0.324$, $p < 0.01$), ABPHT ($r = 0.274$, $p < 0.01$), CBPHT ($r = 0.260$, $p < 0.05$), NT ($r = -0.247$, $p < 0.05$), and SHT ($r = 0.274$, $p < 0.01$). As for intra-renal vascular lesions, ILA was significantly correlated with age ($r = 0.467$, $p < 0.01$) and eGFR ($r = -0.347$, $p < 0.01$). AH was significantly correlated with age ($r = 0.488$, $p < 0.01$), male sex ($r = 0.218$, $p < 0.05$), smoking ($r = 0.241$, $p < 0.05$), total cholesterol ($r = 0.279$, $p < 0.01$), ABPHT ($r = 0.436$, $p < 0.01$), CBPHT ($r = 0.249$, $p < 0.01$), NT ($r = -0.417$, $p < 0.01$), MHT ($r = 0.305$, $p < 0.01$), and SHT ($r = 0.238$, $p < 0.05$). In the multivariate analysis, SG and IF were significantly correlated with eGFR and urinary protein. ILA was significantly correlated only with age, whereas AH was significantly correlated with age and ABPHT.

Table 3. Univariate analysis between renal histopathology and clinical characteristics

	SG		IF		ILA		AH	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Age	-0.021	0.842	-0.139	0.191	0.467	< 0.01	0.488	< 0.01
Sex (male)	0.160	0.133	0.162	0.127	-0.090	0.398	0.218	< 0.05
BMI	-0.025	0.813	-0.128	0.230	-0.147	0.167	0.162	0.126
Smoking	0.221	< 0.05	0.234	< 0.05	0.044	0.683	0.241	< 0.05
eGFR	-0.542	< 0.01	-0.554	< 0.01	-0.347	< 0.01	-0.195	0.066
CRP	-0.040	0.705	-0.075	0.484	0.043	0.689	0.111	0.298
T-chol	0.202	0.056	0.089	0.404	0.065	0.544	0.279	< 0.01
Urinary protein	0.239	< 0.05	0.324	< 0.01	-0.005	0.965	0.203	0.055
ABPHT	0.234	< 0.05	0.274	< 0.01	0.033	0.758	0.436	< 0.01
CBPHT	0.266	< 0.05	0.260	< 0.05	0.022	0.838	0.249	< 0.05
NT	-0.258	< 0.05	-0.247	< 0.05	-0.005	0.966	-0.417	< 0.01
WHT	0.078	0.464	-0.062	0.564	-0.076	0.476	-0.031	0.770
MHT	0.057	0.593	0.092	0.390	0.036	0.738	0.305	< 0.01
SHT	0.260	< 0.05	0.274	< 0.01	0.002	0.984	0.238	< 0.05

SG: sclerotic glomeruli, IF: interstitial fibrosis, ILA: intimal thickening of intra-lobular arteries, AH: arteriolar hyalinosis, BMI: body mass index, eGFR: estimated glomerular filtration rate, CRP: C reactive protein, T-chol: total cholesterol, ABPHT : hypertension based on ambulatory blood pressure, CBPHT: hypertension based on clinic blood pressure, NT: normotension, WHT: white coat hypertension, MHT: masked hypertension, SHT: sustained hypertension

Table 4. Multivariate analysis between renal histopathology and clinical characteristics

	SG		IF		ILA		AH	
	β	*p*	*β*	*p*	*β*	*p*	*β*	*p*
Age	-	-	-	-	0.390	< 0.01	0.418	< 0.01
Sex (male)	-	-	-	-	-	-	0.160	0.120
Smoking	0.137	0.136	0.137	0.118	-	-	0.090	0.345
eGFR	-0.485	< 0.01	-0.494	< 0.01	-0.165	0.121	-	-
T-chol	-	-	-	-	-	-	0.085	0.908
Urinary protein	0.186	< 0.05	0.266	< 0.01	-	-	-	-
ABPHT	-0.019	0.855	0.009	0.928	-	-	0.218	< 0.05
CBPHT	0.076	0.456	0.046	0.638	-	-	0.015	0.880

GS: sclerotic glomeruli, IF: interstitial fibrosis, ILA: intimal thickening of intra-lobular arteries, AH: arteriolar hyalinosis, eGFR: estimated glomerular filtration rate, T-chol: total cholesterol, ABPHT: hypertension based on ambulatory blood pressure, CBPHT: hypertension based on clinic blood pressure

Discussion

Our study demonstrated the following: (1) among patients with CGD, the prevalence of WHT and MHT was 3.3% and 23.3%, respectively; (2) nighttime HT was most prevalent in the MHT group, whereas all-day HT was most prevalent in the SHT group; (3) the MHT group, as well as the SHT group, had more severe AH than the NT group, but there was no significant difference in ILA among all four groups; and (4) ILA was significantly correlated only with age, whereas AH was significantly correlated with age and ABPHT but not CBPHT.

HT is an important risk factor for the development of CVD and CKD, and it is also a major complication of CKD in its early stages [1]. Furthermore, it is well known that patients with CKD commonly have circadian rhythm BP disorders [7]. Therefore, an accurate diagnosis and control of HT are necessary for patients with CKD in the clinical setting. Among non-invasive BP monitoring methods, CBP measurement underestimated the true BP, whereas ABP and home BP (HBP) were much better correlated with target organ damage than CBP [7, 18]. The relationship between ABP and renal outcome and CVD events has been proved mainly

by longitudinal cohort studies. Agarwal *et al* demonstrated that ABP was an independent risk factor for end stage renal disease, even after adjusting for CBP [6]. In addition, there was accumulating evidence that MHT was an independent risk factor for developing CKD and CVD [19]. However, little is known about the influence of circadian rhythm BP disorder on intra-renal damage. Therefore, we investigated its relationship in patients who had CGD diagnosed by renal biopsy. To exclude the effect of antihypertensive agents, the patients who took antihypertensive treatment were excluded in the present study.

The prevalence of situational HT, such as WHT and MHT, varies among previous studies [12, 13, 20, 21]. In the general population, the prevalence of WHT and MHT was reported to be 15.6% and 10%, respectively [12, 22]. In a CKD population, a meta-analysis by Bangash *et al* among six studies showed that the prevalence ranged from 10.5% to 31.7 % for WHT and from 4.7% to 31.3% for MHT [13]. Japanese cohort studies demonstrated that the prevalence of WHT and MHT in CKD populations were 5.6%–15.4% and 15%–30.9%, respectively [18, 23]. However, there were no previous studies that showed the prevalence of situational HT in CGD. The present study showed that the prevalence of WHT and MHT were 3.3% and 23%, respectively. Our prevalence of MHT was equivalent to that of MHT in a CKD population with decreased kidney function; however, the prevalence of WHT was relatively small in the present study population. The predictors of WHT were considered to be age, female gender, high BMI, and CVD [24]. Therefore, we speculated that the relatively small prevalence of WHT in the present study may be attributed to the inclusion of patients who were relatively young and had low risk for CVD. In addition, the circadian BP pattern that we demonstrated in the present study suggested that nocturnal HT could partly contribute to the underestimation of BP. Therefore, careful BP assessment using ABP monitoring should be performed in the CGD.

The relationship between situational HT and CVD has been reported. Recently, compared with NT, WHT in patients under antihypertensive therapy was recognized to be a slightly higher risk factor for CVD, although not to a similar extent as that for SHT; this risk in patients without antihypertensive therapy is controversial [25]. On the other hand, there are many reports that demonstrated the association between MHT and CVD regardless of the status of treatment [8-11]. However, there are a few reports that demonstrated the association between MHT and renal outcome [26-28]. The Ohasama study, a large cross-sectional cohort study of the general Japanese population using HBP and ABP monitoring, demonstrated that the odds ratio for CKD was significantly higher in patients with MHT and SHT than in patients with NT [23, 29]. Among some recent longitudinal studies on CKD populations, Boggia *et al* showed that the risks for ESRD and mortality were significantly higher in patients with MHT and SHT than in patients with NT and WHT [11]. Furthermore, Minutolo *et al* also reported that MHT posed a higher risk for the progression of CKD and CVD than NT [30]. However, there were no reports that investigated the association between MHT and intra-renal damage. Interestingly, the present study demonstrated that among the findings of renal histopathology, renal AH was more severe in the MHT group as well as the SHT group compared with the NT and WHT groups, and ILA was comparable between all four groups. Furthermore, multivariate analysis showed that renal AH was significantly correlated with age and ABPHT, whereas ILA was significantly correlated only with age. To our knowledge, renal vasculature is characterized to branch from relatively large-sized arteries to small-sized arteries. Such micro-vessels that directly branch from large arteries are called “strain vessels” and are likely to have pressure-induced vascular injury [31]. Therefore, it is possible that the renal arterioles were mainly affected by HT in the present study. Although we showed that nighttime HT was most prevalent in the MHT group, the association between renal arteriolosclerosis and nocturnal HT remains unknown. In patients with nighttime HT and all-day HT, renal arteriolosclerosis tended to be more severe compared with those with NT (data not shown). There is a previous study that demonstrated that endothelial function was impaired in non-dippers compared with dippers [32]. Arterioles are considered to be susceptible to pressure variability and pressure load and conversely, arteriolosclerosis induces the impairment of BP variability and HT through the

stimulation of the renin angiotensin system and sympathetic nerve activity. Recently, Kario *et al* suggested that such a vicious cycle led to the development of organ damage, which was called as systemic hemodynamic atherothrombotic syndrome (SHATS) [33]. In addition, the duration of HT also can influence vascular changes. The present study included only patients without antihypertensive therapy, and most of the study participants did not routinely check BP. Therefore, unfortunately we could not have more precise information about the onset of HT in each patient. However, their BP was not so high, and the duration of HT was not so long because the onset of GD was not a long time ago in most of the hypertensive patients. Taken together, we speculated the influence of HT duration on renal histological changes was not so strong in the present study. On the other hand, it was reported that renal arteriolosclerosis was more commonly observed even in the absence of HT, particularly in IgA nephropathy compared with non-IgA nephropathy [34]. A possible explanation would be that renal arteriolosclerosis could be related to an immune-complex reaction and oxidative stress in glomerulonephritis [35, 36]. Though we could not examine this relationship in the present study, the progression of arteriolosclerosis could be partially mediated by such factors other than HT.

Among the other findings of renal histopathology, SG and IF were significantly more severe in the SHT group, but not in the MHT group, compared with the NT group. Furthermore, univariate analysis demonstrated that SG and IF were significantly correlated with ABPHT and CBPHT. A recent report demonstrated that renal fibrosis was significantly correlated with ABP [37]. However, in our study, multivariate analysis revealed that SG and IF were significantly correlated with urinary protein and eGFR but not with ABPHT and CBPHT. Considering these results, there is a possibility that SG and IF could be influenced by GD, rather than HT, because of heterogenecity in the causes of CGD in the present study population.

There were some limitations in the present study. First, we could not establish a cause–effect relationship because of the cross-sectional study design. The present study-included the patients with various histological diagnosis of GD and various kidney function. However, the number of the study patients was not enough to perform stratified analysis for each type of GD and each stage of kidney function. Furthermore, we consider that it's also difficult to perform the longitudinal design. Second, the number of study participants was relatively small, and the proportion of patients with HT was 40% among the study population. Therefore, the number of patients with WHT was particularly small. However, to exclude the influence of HT treatments, patients on antihypertensive agents were excluded in the present study. Third, the precise duration of GD was not clear in the present study because it is difficult to know the onset of GD. We defined "chronicity" as persistent urinalysis abnormalities for at least 3 months. Finally, ABP monitoring was performed only once in each patient, therefore we could not ensure the reproducibility of the ABP recordings. Many previous studies have already proven that ABP monitoring was a much stronger predictor of target organ damage compared with CBP, and the results of the present study were consistent with these findings.

Conclusion

MHT as well as SHT could be the predictors of intra-renal AH. Careful ABP monitoring should be recommended in patients with CGD.

Disclosure Statement

All the authors declared no competing interests.

Acknowledgments

We thank Shigeo Hara for renal histopathological assessment. This study was partially presented in Kidney Week 2013, American Society of Nephrology.

References

1 Rao MV, Qiu Y, Wang C, Bakris G: Hypertension and CKD: Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES), 1999–2004. Am J Kidney Dis 2008;51:S30-S37.
2 Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, Ford CE, Shulman NB, Stamler J: Blood pressure and end-stage renal disease in men. N Engl J Med 1996;334:13-18.
3 Reynolds K, Gu D, Muntner P, Kusek JW, Chen J, Wu X, Duan X, Chen CS, Klag MJ, Whelton PK, He J: A population-based, prospective study of blood pressure and risk for end-stage renal disease in China. J Am Soc Nephrol 2007;18:1928-1935.
4 Yamagata K, Ishida K, Sairenchi T, Takahashi H, Ohba S, Shiigai T, Narita M, Koyama A: Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. Kidney Int 2007;71:159-166.
5 Sarafidis PA, Li S, Chen SC, Collins AJ, Brown WW, Klag MJ, Bakris GL: Hypertension awareness, treatment, and control in chronic kidney disease. Am J Med 2008;121:332-340.
6 Agarwal R, Andersen MJ: Prognostic importance of ambulatory blood pressurerecordings in patients with chronic kidney disease. Kidney Int 2006;69:1175-1180.
7 Agarwal R: Ambulatory blood pressure and cardiovascular events in chronic kidney disease. Semin Nephrol 2007;27:538-543.
8 Farmer CK, Goldsmith DJ, Cox J, Dallyn P, Kingswood JC, Sharpstone P: An investigation of the effect of advancing uraemia, renal replacement therapy and renal transplantation on blood pressure diurnal variability. Nephrol Dial Transplant 1997;12:2301-2307.
9 Ohkubo T, Kikuya M, Metoki H, Asayama K, Obara T, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y: Prognosis of "masked hypertension" and "white-coat" hypertension detected by 24-h ambulatory blood pressure monitoring 10-year follow-up from the Ohasama study. J Am Coll Cardiol 2005;46:508-515.
10 Yano Y, Kario K: Nocturnal blood pressure and cardiovascular disease: a review of recent advances. Hypertens Res 2012;35:695-701.
11 Boggia J, Silvarino R, Luzardo L, Noboa O: Significance of white-coat and masked hypertension in chronic kidney disease and end-stage renal disease. Hypertens Res 2014;37:882-889.
12 Pickering TG, Eguchi K, Kario K: Masked hypertension: a review. Hypertens Res 2007;30:479-488.
13 Bangash F, Agarwal R. Masked hypertension and white-coat hypertension in chronic kidney disease: a meta-analysis. Clin J Am Soc Nephrol 2009;4:656-664.
14 JCS Joint Working Group: Guidelines for the clinical use of 24 hour ambulatory blood pressure monitoring (ABPM) (JCS 2010):-digest version-. Circ J 2012;76: 508-519.
15 Parati G, Stergiou G, O'Brien E, Asmar R, Beilin L, Bilo G, Celement D, de la Sierra A, de Leeuw P, Dolan E, Fagard R, Graves J, Head GA, Imai Y, Kario K, Lurbe E, Mallion JM, Mancia G, Mengden T, Myers M, Ogedegbe G, Ohkubo T, Omboni S, Palatini P, Redon J, Ruilope LM, Shennan A, Staessen JA, vanMontfrans G, Verdecchia P, Waeber B, Wang J, Zanchetti A, Zhang Y; European Society of Hypertension Working Group on Blood Pressure Monitoring and Cardiovascular Variability: European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. J Hypertens 2014;32:1359-1366.
16 Shimamoto K, Ando K, Fujita T, Hasebe N, Higaki J, Horiuchi M, Imai Y, Imaizumi T, Ishimitsu T, Ito M, Ito S, Itoh H, Iwao H, Kai H, Kario K, Kashihara N, Kawano Y, Kim-Mitsuyama S, Kimura G, Kohara K, Komuro I, Kumagai H, Matsuura H, Miura K, Morishita R, Naruse M, Node K, Ohya Y, Rakugi H, Saito I, Saitoh S, Shimada K, Shimosawa T, Suzuki H, Tamura K, Tanahashi N, Tsuchihashi T, Uchiyama M, Ueda S, Umemura S; Japanese Society of Hypertension Committee for Guidelines for the Management of Hypertension: The Japanese society of hypertension guidelines for the management of hypertension (JSH 2014). Hypertens Res 2014;37:253-387.

17 Pokorna E, Vitko S, Chadimova M, Schuck O: Adverse effect of donor arteriolosclerosis on graft outcome after renal transplantation. Nephrol Dial Transplant 2000;15:705-710.
18 Thompson AM, Pickering TG: The role of ambulatory blood pressure monitoring in chronic and end-stage renal disease. Kidney Int 2006;70:1000-1007.
19 Ogedegbe G, Agyemang C, Ravenell JE: Masked hypertension: Evidence of the Need to Treat. Curr Hypertens Rep 2010;12:349-355.
20 Iimuro S, Imai E, Watanabe T, Nitta K, Akizawa T, Matsuo S, Makino H, Ohashi Y, Hishida A, for the Chronic Kidney Disease Japan Cohort Study Group: Clinical correlates of ambulatory BP monitoring among patients with CKD. Clin J AmSoc Nephrol 2013;8:721-730.
21 Gorostidi M, Vinyoles E, Banegas JR, de la Sierra A: Prevalence of white-coat and masked hypertension in national and international registries. Hypertens Res 2015;38:1-7.
22 Martin CA, McGrath BP: White-coat hypertension. Clin Exp Pharmacol Physiol 2014;41:22-29.
23 Kanno A, Metoki H, Kikuya M, Terawaki H, Hara A, Hashimoto T, Asayama K, Shishido Y, Nakayama M, Totsune K, Ohkubo T, Imai Y: Usefulness of assessing masked and white-coat hypertension by ambulatory blood pressure monitoring for determining prevalent risk of chronic kidney disease: the Ohasama study. Hypertens Res 2010;33:1192-1198.
24 Manios ED, Koroboki EA, Tsivgoulis GK, Spengos KM, Spilopoulou IK, Brodie FG, Vemmos KN, Zakopoulos NA: Factors influencing white-coat effect. Am J Hypertens 2008;21:1153-1158.
25 Franklin SS, Thijs L, Hansen TW, O'Brien E, Staessen JA: White-coat hypertension: new insights from recent studies. Hypertension 2013;62:982-987.
26 Fukuhara M, Arima H, Ninomiya T, Hata J, Hirakawa Y, Doi Y, Yonemoto K, Mukai N, Nagata M, Ikeda F, Matsumura K, Kitazono T, Kiyohara Y: White-coat and masked hypertension are associated with carotid atherosclerosis in a general population: the Hisayama study. Stroke 2013;44:1512-1517.
27 Bobrie G, Chatellier G, Genes N, Clerson P, Vaur L, Vaisse B, Menard J, Mallion JM: Cardiovascular prognosis of " masked hypertension" detected by blood pressure self-measurement in elderly treated hypertensive patients. JAMA 2004;291:1342-1349.
28 Pickering TG, Eguchi K, Kario K: Masked hypertension: a review. Hypertens Res 2007;30:479-488.
29 Terawaki H, Metoki H, Nakayama M, Ohkubo T, Kikuya M, Asayama K, Inoue R, Hoshi H, Ito S, Imai Y: Masked hypertension determined by self-measured blood pressure at home and chronic kidney disease in the Japanese general population: The Ohasama study. Hypertens Res 2008;31:2129-2135.
30 Minutolo R, Gabbai FB, Agarwal R, Chiodini P, Borrelli S, Bellizzi V, Nappi F, Stanzione G, Conte G, De Nicola L: Assessment of achieved clinic and ambulatory blood pressure recordings and outcomes during treatment in hypertensive patients with CKD: A multicenter prospective cohort study. Am J Kidney Dis 2014;64:744-752.
31 Ito S, Nagasawa T, Abe M, Mori T: Strain vessel hypothesis: a viewpoint for linkage of albuminuria and cerebro-cardiovascular risk. Hypertens Res 2009;32:115-121.
32 Higashi Y, Nakagawa K, Kimura M, Noma K, Hara K, Sasaki S, Goto C, Oshima T, Chayama K, Yoshizumi M: Circadian variation of blood pressure and endothelial function in patients with essential hypertension: a comparison of dippers and non-dippers. J Am Coll Cardiol 2002;40:2039-2043.
33 Kario K: Orthostatic hypertension-a new haemodynamic cardiovascular risk factor. Nat Rev Nephrol 2013;9:726-738.
34 Wu J, Chen X, Xie Y, Yamanaka N, Shi S, Wu D, Liu S, Cai G: Characteristics and risk factors of intrarenal arterial lesions in patients with IgA nephropathy. Nephrol Dial Transplant 2005;20:719-727.
35 Kojima C, Takei T, Ogawa T, Nitta K: Serum complement C3 predicts renal arteriolosclerosis in non-diabetic chronic kidney disease. J Atheroscler Thromb 2012;19:854-861.
36 Fujii H, Kono K, Nakai K, Goto S, Kitazawa R, Fukagawa M, Nishi S: Renin-Angiotensin system inhibitors reduce serum asymmetric dimethylarginine levels and oxidative stress in normotensive patients with chronic kidney disease. Nephron Extra 2014;4:18-25.
37 Haruhara K, Tsuboi N, Koike K, Fukui A, Miyazaki Y, Kawamura T, Ogura M, Yokoo T: Renal histopathological findings in relation to ambulatory blood pressure in chronic kidney disease patients. Hypertens Res 2014;38:116-122.