Evaluation of 24 h ambulatory blood pressure in chronic kidney disease patients with normal casual blood pressure.

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Abstract

The aim of this study was to evaluate the 24 h Ambulatory Blood Pressure (ABP) in Chronic Kidney Disease (CKD) patients with normal Casual Blood Pressure (nCBP). A total of 350 nCBP-CKD patients (phases 1-5), with 136 men and 214 women, were selected, and the 24 h ABP was monitored using one Spacelabs noninvasive portable ABP monitor. In 350 nCBP-CKD patients, 147 exhibited increased mean ABP, accounting for 42% (147/350), but some patients exhibited only nocturnal ABP increase; 69 patients exhibited masked hypertension, accounting for 19.7% (69/350); 199 patients exhibited abnormal Blood Pressure Model (BPM) (circadian rhythm disappearing), accounting for 56.9% (199/350); 204 patients exhibited increased Blood Pressure Load (BPL), accounting for 58.3% (204/350), among which nocturnal BPL increase accounted for the main part. The 24 h ABP and mean nycterohemeral blood pressure in patients with high CBP were significantly higher than those in patients with normal CBP and healthy controls, respectively (P<0.01). CKD patients with normal CBP exhibit situations such as mean ABP increase, masked hypertension, nocturnal hypertension, and BPL and BPM abnormalities.

Introduction

Chronic Kidney Disease (CKD) is a global public health problem with high morbidity and mortality, and some CKD patients will eventually enter End-Stage Renal Disease (ESRD) [1,2]. CKD occurs because of different causes, and good CKD prevention will help reduce the occurrence of ESRD. A cross-sectional study based on Hispanic and Latin-American adults in the USA showed the prevalence of CKD as 13.7% in men and 13% in women [3]. One cross-sectional study in different Chinese provinces and cities showed the prevalence of CKD as 10.8% [4]. It was considered that the prevalence of CKD in populations is 10% to 15%. CKD can increase the risk of Cardiovascular Diseases (CVD) [3,5]. One multicenter non-dialysis CKD study in China showed that the prevalence of hypertension is 67.3% and the control rate is 33.1% (Blood Pressure (BP)<140/90 mmHg) [6]. Certain literature has suggested that the prevalence of hypertension in patients undergoing dialysis and kidney transplantation is 80% to 90% [7]. Kidneys are the target organ of hypertension as well as the initiating organ of renal hypertension; it is well known that

hypertension is related to the occurrence and progression of CKD. Studies have shown that the incidence of renal dysfunction in CKD patients combined with hypertension is 16.8% (using serum cystatin as the evaluation criterion) and 8.9% (using serum creatinine as the evaluation criterion) [8]; a Japanese study showed that prehypertension is related to CKD and is one of the causes of CKD [8]. Reasonable BP control is important in delaying renal dysfunction, protecting the kidneys, preventing ESRD, and reducing cardiovascular risks. Hypertension and CKD usually co-exist, and both are risk factors for cardiovascular events and death. Ambulatory Blood Pressure (ABP) can more comprehensively reflect the conditions of patients' BP control than Casual Blood Pressure (CBP), and it can particularly display the circadian rhythm of BP, the existence of nocturnal hypertension, or masked hypertension (MHT); as for reflecting the progression of CKD and end-organ damages, ABP is better than CBP [9,10]. The clinical reports about the conditions of ABP in nCBP-CKD patients are few. To investigate the characteristics of ABP in nCBP-CKD patients, we chose a total of 350 nCBP-CKD patients (phases 1-5) for the study, aiming to provide scientific

basis for the prevention and treatment of CKD. The results are reported as follows.

Materials and Methods

Subjects

A total of 350 CKD patients (phases 1-5) being treated in our hospital and having nCBP were selected, among whom, a majority were outpatients and a small percentage were inpatients. The diagnosis and staging of CKD referred to the definition and staging criteria in the "Clinical Practice Guidelines of Kidney Disease/Dialysis" proposed by the Kidney Disease Outcomes Quality Initiative (KDOQI) work group, National Kidney Foundation (NKF), USA [11]. The included 350 patients were divided into two groups according to their CBP levels: group 1 included the patients with normal CBP (BP<120/80 mmHg), and group 2 included the patients with nCBP at high values (BP 120-139/80-89 mmHg). Meanwhile, 50 healthy persons were selected as the control group, with an average age of 62.6 ± 11.5 y. Groups 1 and 2 had no statistically significant difference in the age and gender composition. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Fudan University. Written informed consent was obtained from all participants.

Group 1 had 146 patients, 58 men and 88 women, aging 61.9 ± 14.0 y, including 47 patients in CKD phase 1 (32.2%), 46 patients in CKD phase 2 (31.5%), 36 patients in CKD phase 3 (24.6%), 14 patients in CKD phase 4 (9.6%), and 3 patients in CKD phase 5 (2.1%). The primary diseases were chronic pyelonephritis in 34 patients, IgA nephritis in 31 patients, hypertensive nephropathy in 29 patients, chronic nephritis in 18 patients, chronic interstitial nephritis in 10 patients, diabetic nephropathy and ischemic nephropathy in 6 patients each, renal arteriosclerosis in 5 patients, gouty nephropathy and tumor-associated nephropathy in 2 patients, and aristolochic acid-related nephropathy, purpura nephritis, and obstructive nephropathy in 1 patient each. The average disease duration was 85.46 ± 127.03 months.

Group 2 had 204 patients, 78 men and 126 women, aging 63.4 ± 14.4 y, including 60 patients in CKD phase 1 (29.4%), 70 patients in CKD phase 2 (30.3%), 55 patients in CKD phase 3 (26.9%), 14 patients in CKD phase 4 (6.9%), and 5 patients in CKD phase 5 (2.5%). The primary diseases were hypertensive nephropathy in 54 patients, chronic pyelonephritis in 40 patients, IgA nephritis in 35 patients, chronic nephritis in 27 patients, diabetic nephropathy in 19 patients, chronic interstitial nephritis in 13 patients, renal arteriosclerosis in 5 patients, gouty nephropathy in 3 patients, solitary kidney and renal atrophy in 2 patients each, and obstructive nephropathy, anodyne-induced nephropathy, and renal calculus in 1 patient each. The average disease duration was 69.58 ± 89.76 months.

The control group (C) had 50 healthy persons (25 men and 25 women) had normal BP (physical examination) and excluded

cardiovascular and renal diseases by appropriate examinations, with the mean age as 62.6 ± 11.5 y.

Inclusion and exclusion criteria

The inclusion criteria were nCBP-CKD (phases 1-5), absence of hypertension (154 patients), and controlled BP within normal ranges for more than a month after treatment (196 patients). The anti-hypertensive medication was taken by 196 CKD patients. Among them, 76 patients took one drug (CCB, ACEI, or ARB); 89 patients, two drugs (CCB combined with ACEI and ARB or β-blockers); 31 patients, three drugs or more (three or more anti-hypertensive drugs were combined from five categories of anti-hypertensive agents). All patients took the drug in the morning, but nine patients took it in the morning and evening.

The exclusion criteria were CBP increase while not receiving any treatments or hypertension after treatment; control of BP but exhibiting CBP increase on the day of ABP measurement; qualification rate of ABP less than 80% and not reaching the standards on re-monitoring.

Measurement of CBP

CBP measurement, also known as the office BP, uses a standard mercury sphygmomanometer, with the systolic BP taking the first Korotkoff sound and the diastolic BP taking the fifth Korotkoff sound. During the measurement, each patient is required to rest for 10 min, and then the measurement is taken twice (time interval, 1 min) in the sitting position. Six CBP values measured on the day of ABP measurement (once) as well as two weeks before the day of ABP measurement (twice) were averaged and used as the patient's CBP; each measurement was taken on the same upper arm. According to the literature [12,13], BP<120/80 mmHg was defined as nCBP, BP 120-139/80-89 mmHg was defined as nCBP with high value, and BP ≥ 140/90 mmHg was defined as hypertension.

Measurement of ABP

The 24 h ABP was monitored using one Spacelabs 90207 noninvasive portable ABP monitor (made in the Spacelabs company of USA), with the cuff inflation pressure adjusted automatically within 5.32-34.5 kPa (40-259 mmHg). The automatic adjustment was set as once every 30 min in the daytime and once every 60 min at night; the monitoring time was not less than 23 h, and the daytime-nighttime allocation was 6:00-22:00 (daytime) and 22:00-6:00 (nighttime). Effective monitoring times within 24 h should not be less than 80% of the counts, and each subject generally can have 32-40 groups of data, including SBP, DBP, BPL, and Mean Arterial Pressure (MAP). The reference values of normal average ABP were 24 h BP<130/80 mmHg, diurnal ABP (dABP)<135/85 mmHg, and nABP<120/70 mmHg; normal BPL<10% (expressed as the percentage of SBP and DBP that exceeded normal ranges in a certain time); circadian rhythm (dMAP-nMAP/dMAP) × 100%; <10% indicated the disappearing of

the dipper curve, non-dipper-like, and >10% indicated the existence of the dipper curve, dipper-like [14-16].

Statistical analysis

SPSS 16.0 software was used. When the measurement data were normally distributed, it was expressed as mean ± standard deviation; the comparison of the data among groups used the variance analysis. When the measurement data were non-normally distributed, it was expressed as the Median (M) and twenty-fifth and seventy-fifth of percentile representation (P25, P75). The comparison of the data among groups used the Wilcoxon-Mann-Whitney test. The count data were expressed as frequency (n) and percentage (%) and compared using the χ^2 test, with P-value<0.05 considered as statistically significant difference.

Results

MHT and Abnormal BPM

In this study, we found that, with setting nCBP<140/90 mmHg and daytime ABP increasing ≥ 135/85 mmHg as the diagnostic criteria of MHT [14], the prevalence of MHT was 19.7% (69/350). Among the CKD patients, the prevalence of MHT was 9.7% (15/154) in those without a history of hypertension but 27.6% (54/196) in those with a history of hypertension. This was a statistically significant difference (P<0.01); meanwhile, it was also found that the prevalence of MHT was 11.2% (16/143) in group 1 and 25.9% (53/205) in group 2. This was also a statistically significant difference (P<0.01). A certain study also used 24-h ABP as the diagnostic criterion of MHT [17]; so, if the above two criteria were combined together and set as the diagnostic criteria of MHT, the prevalence of MHT in this study would reach 27.7% (97/350).

In addition to 69 patients of MHT, the other 281 CKD patients exhibited simultaneous increase of both 24 h ABP and mean nABP (6.4%) in 18 patients, only 24 h ABP increase (0.07%, daytime and nABPs were normal) in 2 patients, and only nABP increase (20.6%) in 58 patients. A total of 147 patients exhibited an increase in mean ABP, accounting for 42%.

Abnormal BPM and BPL

In this study, the incidence of abnormal BPM in these CKD patients was high (199/350, 56.9%), showing CRD and non-dipper-like change, especially in those with normal CBP and ABP as well as without a history of hypertension, reaching 47.2%, and 51 patients showed CRD; among these patients, the incidence of abnormal BPL was 30.6% (33/108), followed by nDBPL, nSBPL, dSBPL, and dDBPL increase. Certain literature set>25% as the criterion of BPL increase [18], and this study also used this criterion to determine whether BPL increased. In order to facilitate the statistics, the time segment with the maximum BPL increase in each patient (three time segments: 24 h, daytime, or nighttime) was set as the standard to calculate the BPL increase. Among all patients, 58.3% exhibited BPL increase (204/350), and among these patients, 66 patients exhibited nSBPL increase, and 68 patients exhibited nDBPL increase (a total of 134 patients exhibited nBPL increase, accounting for 65.7%); 49 patients exhibited dSBPL increase, and 21 patients exhibited dDBPL increase (a total of 70 patients exhibited dBPL increase, accounting for 34.3%).

In this study, only 4 patients exhibited CRD in the control group (8%) and showed statistically significant difference with those in groups 1 and 2 (P<0.01). The detailed data of the three groups are shown in Tables 1 and 2.

Table 1. *Comparison of CBP and ABP among the three groups ($\bar{x} \pm s$).*

Group	CBP		24 h ABPM		Mean dBP		Mean nBP (mmHg)	
	SBP	DBP	24 h SBP	24 h DBP	dSBP	dDBP	nSBP	nDBP
C (n=50)	122.5 ± 10.7	77.9 ± 6.0	113.0 ± 6.7	67.8 ± 4.8	116.6 ± 6.9	70.8 ± 5.5	100.7 ± 7.1	58.8 ± 4.9
1 (n=146)	112.0[a] ± 8.1	72.9[a] ± 5.6	115.1 ± 12.3	68.7 ± 7.6	117.0 ± 12.1	70.3 ± 8.3	109.0[a] ± 15.1	63.3[a] ± 8.2
2 (n=204)	128.9[ab] ± 5.4	79.9[ab] ± 6.2	123.3[ab] ± 12.0	72.0[ab] ± 8.4	125.5[ab] ± 12	73.6[ab] ± 8.7	116.2[ab] ± 15	66.3[ab] ± 9.9

Note: [a]P<0.01 *vs.* control; [b]P<0.01 *vs.* group 1.

Table 2. *Comparison of BP load among the three groups (M (P_{25}, P_{75}), %).*

Group	24 h BPL (%)		dBPL (%)		nBPL (%)	
	24 h SBPL	24 h DBPL	dSBPL	dDBPL	nSBPL	nDBPL
C (n=50)	5.1 (2.5, 12.1)	3.0 (0.0,7.0)	6.2 (0.0, 14.4)	3.3 (0.0, 9.0)	0.0 (0.0, 12.5)	0.0 (0.0, 9.4)
1 (n=146)	5.0 (0.0, 20.5)	5.1 (0.0, 13.1)	3.6 (0.0, 19.4)	3.4 (0.0, 10.3)	0.0 (0.0, 18.1)[ac]	3.6 (0.0, 25.0)[ad]
2 (n=204)	20.6 (7.9, 38.7)[ab]	10.6 (2.6,27.9)[ab]	19.2 (6.3, 38.7)[ab]	7.0 (0.0, 27.6)[ab]	18.1 (0.0, 38.1)[abc]	12.5 (0.0, 38)[abd]

Note: [a]P<0.01 *vs.* Control; [b]P<0.01 *vs.* Group 1; [c]P<0.01 dSBPL *vs.* nSBPL in the same group; [d]P<0.01 dDBPL *vs.* nDBPL in the same group.

Discussion

This study selected a total of 350 nCBP-CKD patients with different causes and in different stages (among whom 154 patients had no history of hypertension and had normal BP at the entry, and 196 patients had a history of hypertension but controlled within the normal range). The results revealed 147 patients with ABP increase, accounting for 42% of all patients (appearing as mean dBP increase in 69 patients; simultaneous increase of dBP and nBP was exhibited in 55 patients, 24 h ABP and nABP increase in 18 patients, only 24 h ABP increase in 2 patients (the dBP and nBP were normal), and only nABP increase in 58 patients). A total of 69 patients exhibited MHT, accounting for 19.7%; a certain study used 24 h ABP as the diagnostic criterion of MHT [17], and if these two were combined and used as the diagnostic criteria of MHT, the prevalence of MHT in this study was 25.4% (89/350). A total of 199 patients exhibited abnormal BPM (CRD) (56.9%); 204 patients exhibited BPL increase (58.3%), with nBPL increase as the main form (65.7%, 134/204). The 24-h BP, as well as the mean dBP and nBP, in group 2 was significantly higher than those in group 1 and the control group (P<0.01).

It can be seen from Table 1 that the 24 h BP (SBP and DBP) and mean dBP and nBP in group 2 were significantly higher than those in group 1 and in the control group (P<0.01); although nCBP in group 1 was lower than those in the control group, its nBP (nSBP and nDBP) was significantly higher than in the control group (P<0.01). This study found no common phenomenon that the nBP in hypertensive patients is higher than their dBP, which may be related to the selected patients who had already controlled their BP or had no history of hypertension. Table 2 shows that the 24 h BPL (SBPL and DBPL), dBPL, and nBPL in group 2 was significantly higher than that in group 1 and the control group (P<0.01). The nBPL in group 1 was significantly higher than in the control group (P<0.01), and the dSBPL was significantly higher than the nSBPL in the two CKD groups (P<0.01), whereas the dDBPL was significantly lower than the nDBPL in the same groups (P<0.01).

Among the 154 CKD patients without a history of hypertension, 46 patients exhibited ABP increase (29.9%), specifically shown as 15 patients of dABP increase (also known as MHT), with the prevalence at 9.7%; among these 15 patients, 11 patients also exhibited nBP increase. Nine patients exhibited an increase of both 24 h ABP and nABP (5.8%), and 22 patients exhibited only nBP increase (14.3%), among whom, six patients exhibited nSBP increase, 13 patients exhibited nDBP increase, and three patients exhibited an increase of both. A total of 88 patients exhibited abnormal BPM (57.1%), and it should be noted that, among the 108 patients with both normal CBP and normal ABP, 51 patients (47.2%) exhibited abnormal BPM and 33 patients (30.6%) exhibited BPL increase; a total of 76 patients exhibited BPL increase (49.4%), among whom, 17 patients exhibited dBPL

increase and 59 patients exhibited nBPL increase; nBPL increase accounted for the majority, especially nDBPL.

Among the 196 CKD patients who had a history of hypertension but controlled their BP within the normal range, 101 patients exhibited ABP increase (51.5%), significantly higher than those in patients without a history of hypertension (29.9%, P<0.01). The specific manifestation included dBP increase in 54 patients (among whom, 44 patients also exhibited nBP increase), with the prevalence of MHT as 27.6%, significantly higher than that in group 1 (P<0.01). Nine cases exhibited a simultaneous increase of 24 h ABP and nABP (4.6%), 2 patients exhibited only 24-h ABP increase, and 36 patients exhibited only nABP increase (18.4%), showing no significant difference compared with those in group 1 (22 patients, 14.3%) (P>0.05). Among these patients, 19 patients exhibited nSBP and nDBP increase, 9 patients exhibited nSBP increase, and 8 patients exhibited nDBP increase. A total of 111 patients exhibited abnormal BPM (56.6%), showing no significant difference compared with those in group 1 (88 patients, 57.1%, P>0.05), indicating that having a history of hypertension or not will not generate a difference in the incidence of nocturnal hypertension and abnormal BPM. A total of 128 patients exhibited BPL increase (65.3%), significantly higher than those in group 1 (76 patients, 49.4%, P<0.01). Fifty-three patients exhibited dBPL increase, and 75 patients exhibited nBPL increase, and nBPL increase still accounted for the majority, but nSBPL was higher than nDBPL (50/25). Different from the fact that fewer patients in group 1 exhibited nDBPL increase, this group mainly exhibited SBPL increase (SBPL, 79 patients; DBPL, 49 patients), and nBPL increase was higher than dBPL increase.

It was also found that the prevalence of MHT in group 1 was 11% (16/146) but that in group 2 was 26% (53/204); there was a statistically significant difference between these two groups (P<0.01). It was reported that [9] MHT is common in CKD patients and related to the decrease of glomerular filtration rate, proteinuria, or cardiovascular target organ damage, so it should be paid high attention. It can be seen from Table 1 that nCBP in group 1 was lower than that in the control group, but its nABP (SBP and DBP) was significantly higher (P<0.01). The study did not find the phenomenon of nBP>dBP which is common in hypertensive patients, and it may be related to the selected patients who had already controlled their BP or had no history of hypertension. It is noteworthy that 58 patients in this study only exhibited nABP increase while having normal BP in other time segments; a certain study [19] has named it as solitary nocturnal hypertension, which has a higher incidence in CKD patients and is related to target organ damage. During this study, some patients were re-examined within 3-12 months after the first examination, among which, some nBP returned to normal whereas some still exhibited nocturnal hypertension, and we believe that the patients still having nocturnal hypertension should be given treatment. Huangfu et al. [20]

reported that the same antihypertensive drugs taken by the patients with primary hypertension in the morning or 24 h before sleeping can both reduce their BP, but the latter method exhibited less incidence of BP morning peak and nocturnal hypertension, so the medication time was recommended to be in the evening. Studies [19,21,22] found that nocturnal hypertension is closely related to target organ damage and cardiovascular events in the future and nSBP increase is an independent risk factor for target organ damage, and more and more evidence has proven that the most sensitive predictor of cardiovascular disease and death is nBP.

In this study, the incidence of abnormal BPM (non-dipper-like) was 56.9% (199/350), but the control group only had 4 patients (8%) with CRD, and there was a significant difference between them (P<0.01). Even in the CKD patients with nCBP and ABP without hypertension, 51 patients (47.2%) still exhibited CRD. Our research showed that, as for the CKD patients with or without hypertension, nearly half or more than half of patients may exhibit CRD. Studies [23,24] have reported that CRD (non-dipper-like BP) is common in CKD patients and associated with the increased cardiovascular risks and non-dipper-like BP is closely related to cardiovascular morbidity and mortality, as well as the progression of renal hypofunction. The circadian rhythm of BP is very important in adapting to the body's activities and protecting the normal vascular structures and functions of the heart, brain, and kidneys, and the destruction of the circadian rhythm may be associated with atherosclerosis, target organ damage, or cardiovascular events. Circadian rhythm abnormalities in hypertensive patients are related to kidney damage, among which anti-dipper and ultra-dipper-like types are the most significant. Therefore, CKD patients should not only control their BP well but also change their circadian rhythm abnormalities; one study has shown [23] that the administration of antihypertensive drugs before sleeping at night can control nocturnal hypertension as well as improve the circadian rhythm of BP. This also explains why CKD is a risk factor for cardiovascular and cerebrovascular diseases.

Among all patients in this study, 204 patients exhibited BPL increase (58.3%), among whom, 134 patients exhibited nBPL increase, accounting for 65.7%, and the increased degrees of nSBPL and nDBPL were similar (66/68), indicating that the BPL increase in nCBP-CKD patients mainly occurred at night. A certain study [15] showed that the nASBPL increase is related to target organ damage in non-diabetic CKD patients (left ventricular mass index, glomerular filtration rate, and proteinuria) and independent from ABP. Another study [25] showed that dSBPL increase is related to target organ damage in CKD patients. White et al. [26] also found that 24 h BPL is related positively to the left ventricular mass index but negatively to the left ventricular filling pressure. It is believed that, when SBPL and DBPL reach 40%, they can be used to forecast the left ventricular functional status; when they are >40%, the possibility of left ventricular hypertrophy and left ventricular diastolic dysfunction can be as high as up to 60%-90%. Especially nBPL increase and CRD can keep the heart in a long-term overload status, thus causing left

ventricular hypertrophy and dysfunction. BPL>40% is an early warning value of hypertensive cardiac involvement. Studies [27,28] have found that the patients with prehypertension and hypertension have early systolic and diastolic dysfunction, and this abnormality is related to SBPL, cardiac remodeling, or insulin resistance; hypertensive patients with heart disease exhibit 24 h BPL increase, and this can gradually lead to cardiac dysfunction. The above results suggest that BPL increase is closely related to hypertension and hypertension-associated heart, brain, kidney, and blood vessel damage, so it should be paid high attention.

In summary, this study reveals the significant abnormalities in nCBP-CKD patients (including MHT, nocturnal hypertension, BPL increase, and CRD of BP); therefore, for CKD patients, CBP cannot be used satisfactorily to evaluate whether the patient's BP has been controlled; instead, ABP should be used to comprehensively assess the patient's 24 h BP levels, especially such indices as nBP, BPL, or the circadian rhythm of BP, which are closely related to target organ damage, so as to intervene and control cardiovascular risk factors as early as possible.

In this study, the sample size is small. Moreover, the numbers of CKD4 and CKD5 patients was lesser than those of CKD1 and CKD3 patients; therefore the clinical significance is for reference, and in future, further research is needed with a larger sample size.

Acknowledgements

Conflicts of Interest

The authors declare no conflict of interest.

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