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The Relationship Between Blood Pressure Variability And Renal Progression In Hypertensive Patients With Chronic Kidney Disease

Hipertansif Kronik Böbrek Hastalığı Hastalarında Kan Basıncı Değişkenliği Ve Renal Progresyon Arasındaki İlişki

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ÖZET

Amaç: 24-saatlik sistolik kan basıncı (SKB) ve diyastolik kan basıncı (DKB) değişkenliğinin (KBD), kronik böbrek hastalığı (KBH) olan hipertansiyon (HT) hastalarında renal progresyona etkisini değerlendirmek

Yöntem: Bu çalışmaya 24-saatlik ambulatuvar kan basıncı ölçümü (AKBÖ) verisi mevcut KBH ve hipertansiyon tanılı 59 hasta dahil edildi. SKB, DKB ve SKB ve DKB için KBD katsayıları (DK) olarak sırasıyla SKB-DK ve DKB-DK kaydedildi. hGFH değerinde yılda <5 ml/dk azalma normal renal progresyon, yılda ≥5 ml/dk azalma ise hızlı renal progresyon olarak kabul edildi.

Bulgular: Toplamda, hastaların %40,6'sında kontrolsüz HT, %45,8'inde ise non-dipper patern saptandı. Ortalama (Ort)± standart sapma (SS) gündüz, gece SKB ve SKB-DK değerleri sırasıyla 135,3±17,9 mmHg, 128,6±23,0 mmHg, 11,7±2,8 and 9,5±3,6 olarak bulundu. Ort±SS gündüz, gece DKB ve DKB-DK değerleri sırasıyla 84,5±13,4 mmHg, 77,2±16,1 mmHg, 13,8±3,8 ve 12,0±3,7 idi. Hızlı renal progresyon hastaların %25,4'ünde mevcut olup, hızlı ve doğal renal progresyon grupları arasında gündüz, gece ve toplam SKB, SKB-DK, DKB ve DKB-DK değerleri arasında anlamlı bir fark gözlenmedi. Yaş, cinsiyet, diyabet varlığı, bazal hesaplanmış glomerüler filtrasyon hızı (hGFH) ve dipping paterne göre ayarlanmış regresyon analizi sonuçları SKB-DK ve DKB-DK değerlerinin hızlı renal progresyonu öngördürücü etkisi olmadığı yönünde idi (p> 0.05).

Sonuç: Sonuç olarak, bulgularımız hipertansif KBH hastalarında KBD ile renal progresyon arasında anlamlı bir ilişki olmadığı yönündedir. Bu konunun daha iyi anlaşılabilmesi için daha büyük ölçekli ve daha uzun takip süresine dayanan prospektif, ramdomize kontrollü çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Kan basıncı değişkenliği, hipertansiyon, kronik böbrek hastalığı, renal progresyon

ABSTRACT

Objective: To evaluate the effect of 24 hour systolic blood pressure (SBP) and diastolic blood pressure (DBP) variability (BPV) on renal progression in hypertensive patients with chronic kidney disease (CKD)

Methods: A total 59 hypertensive patients (mean age: 54.2±14.6 years, 50.8% male) with CKD who underwent 24 hours ambulatory blood pressure measurement (ABPM) were included. Data on SBP, DBP, BPV coefficients (VC) for SBP (SBP-CV) and DBP (DBP-CV) were recorded. A decrease in e-GFR of <5 ml/min/year was considered as normal renal progression and a decrease in ≥5 ml/min/year was considered as rapid renal progression.

Results: Overall, 40.6% of the patients had uncontrolled HT, while 45.8% had non-dipper pattern. Mean±SD daytime and night-time SBP and SBP-VC values were 135.3±17.9 mmHg, 128.6±23.0 mmHg, 11.7±2.8 and 9.5±3.6, respectively. Mean±SD daytime and nigh-time DBP and DBP-VC values were 84.5±13.4 mmHg, 77.2±16.1 mmHg, 13.8±3.8 and 12.0±3.7, respectively. Rapid renal progression was detected in 25.4% of patients with no significant difference in daytime, night-time and total SBP, SBP-VC, DBP and DBP-VC values between patients with rapid vs. natural renal progression. The regression analysis adjusted for age, gender, presence of DM, baseline e-GFR and dipping status revealed no significant impact of SBP-VC and DBP-VC in predicting rapid progression (p> 0.05).

Conclusion: In conclusion, our finding revealed no significant association between BPV and renal progression in hypertensive patients with CKD. Larger scale prospective, randomized controlled trials with longer follow-up are needed to clarify this issue.

Keywords: Blood pressure variability, hypertension, chronic kidney disease, renal progression

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Introduction

Hypertension (HT) is one of the most important risk factors in the development of cardiovascular and renal diseases, while hypertensive nephrosclerosis is one of the most important risk factors for development of chronic kidney disease (CKD) and progression to end-stage renal failure (ESRF) (Stamler, et al. 1993: 598; Hsu, et al. 2005: 923).

Ambulatory blood pressure monitoring (ABPM) is recommended in the clinical follow-up of hypertensive patients due to its high reproducibility, independence from the effects of white coat and placebo, allowing to measure nocturnal changes, and prognostic value of night measurements' being higher than daytime measurements (Davidson, et al. 2006: 846; Pickering, et al. 2008: 1; Rothwell, et al. 2010: 895).

Based on ABPM recordings, a decrease of 10% or higher in BP value measured at night compared to daytime value is called "dipping", and no decrease of 10% or higher is called as "non-dipping". Hypertensive individuals are also classified as dipper and non-dipper HT according to the presence of dipping. It is known that the non-dipper HT pattern is associated with earlier and more severe organ damage and increases cardiovascular events and mortality (Davidson, et al. 2006: 846; Rothwell, et al. 2010: 895).

This study was designed to investigate the relationship between blood pressure variability (BPV) and renal progression in patients with chronic kidney disease.

Materials and Methods

A total of 186 adult patients with CKD and HT who were under follow-up for more than 3 months and had 24-hour blood pressure (blood pressure holter) measurements due to various indications were included in this retrospective descriptive study conducted at a tertiary care nephology clinic between January, 1st, 2013 and December, 31st, 2017. Patients who refused to participate in the study, did not follow consecutive day and night ABPM and followed up, for less than 3 months were excluded. After exclusion of 73 patients due to lack of the final e-GFR value, and 54 patients who were followed up for less than 3 months, 59 patients comprised the study population subjected to analysis.

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study which was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the institutional ethics committee.

Blood pressure (BP) and coefficient of variation (CV) were calculated using the formula: SBP-CV: 100* (SBP Standard Deviation/Mean SBP) - DBP-CV: 100*(DBP Standard deviation/Mean DBP).

The average annual decrease (renal progression) in estimated glomerular filtration rate (e-GFR) was accepted as the primary endpoint. The e-GFR values of the patients were calculated by using the CKD-EPI formula. A decrease of <5 ml/min/year in e-GFR was accepted as normal progression, and a decrease of ≥5 ml/min/year as rapid renal progression. Daily proteinuria amount was obtained by calculating the protein/creatinine ratio (mg/gram) in spot urine.

Data on descriptive and clinical characteristics, 24-hour ABPM, BP control and dipping status as well as renal function test results were recorded in each patient. The distribution of 24-hour ABPM measurements and the change in e-GFR values over time were also evaluated with respect to SBP coefficient of variation (SBP-CV) quartile groups.

Results

The mean patient age was 54.2 years (SD 14.6, range, 19 to 76 years) and 50.8% of patients were male patients. Mean±SD duration of follow-up was 15.4 ± 8.0 months. The mean±SD body mass index (BMI) values were 30.9 ± 6.2 kg/m^2. Overall, 39% of patient had diabetes and 23.7% were active smokers (Table 1).

Table 1. Descriptive and clinical characteristics of all patients

Parameter	All patients (n=59)
Age (year), mean±SD (min-max)	54.2±14.6 (19-76)
Gender, n (%)	
Male	30 (50.8)
Female	29 (49.2)
BMI (kg/m2), mean±SD (min-max)	30.9±6.2 (20.1-49.6)
DM, n (%)	23 (39.0)
Smoking, n (%)	14 (23.7)
Follow-up (month), mean±SD (min-max)	15.4±8.0 (3-31)
Calcium Channel Blocker, n (%)	34 (57.6)
Beta-Blocker, n (%)	25 (42.4)
Diuretic, n (%)	21 (35.6)
Angiotensin Receptor Blocker, n (%)	14 (23.7)
ACEI, n (%)	13 (22.0)
Alpha Blocker, n (%)	9 (15.3)
Number of Antihypertensive Medication Use, mean±SD (min-max)	2.0±0.9 (1-4)

n: number of patients; %: Percent; SD: Standard deviation; BMI: Body mass index; CKD: Chronic kidney disease; HT: Hypertension; DM: Diabetes mellitus

24-hour ABPM measurements of all patients are presented in Table 2, while data on blood pressure control and dipping status are presented in Table 3. The distribution of renal function test results at the beginning and end of the follow-up is presented in Table 4.

Table 2. 24-hour ambulatory blood pressure measurements of all patients

Parameter		Mean±SD (min-max)
Systolic Blood Pressure (SBP)		
Daytime (n=59)	SBP	135.3±17.9 (104-184)
	SBP-CV	11.7±2.8 (5.8-18.9)
Night (n=56)	SBP	128.6±23.0 (89-195)
	SBP-CV	9.5±3.6 (4.1-23.2)
Total (n=59)	SBP	134.0±18.4 (101-175)
	SBP-CV	12.0±2.7 (6.1-17.6)
Diastolic Blood Pressure (DBP)		
Daytime (n=59)	DBP	84.5±13.4 (50-110)
	DBP -CV	13.8±3.8 (5.7-26.1)
Night (n=56)	DBP	77.2±16.1 (45-109)
	DBP -CV	12.0±3.7 (4.1-23.1)
Total (n=59)	DBP	82.9±13.9 (49-109)
	DBP -CV	14.3±3.6 (7.1-25.7)

n: number of patients; %: Percent; SD: Standard deviation; SBP: Systolic blood pressure; Std-SBP: Standard systolic blood pressure; SBP-CV: Systolic blood pressure variability coefficient; DBP: Diastolic blood pressure

Table 3. Evaluation of all patients in terms of blood pressure control and dipping status

	Total	SBP < 135 mmHg	DBP < 85 mmHg	Uncontrolled HT	Dipping	
					Dipper	Non-Dipper
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Daytime	59 (100)	31 (52.5)	32 (54.2)			
Night	56 (100)	34 (60.7)	19 (33.9)	24 (40.6)	32 (54.2)	27 (45.8)
Total	59 (100)	35 (59.3)	34 (57.6)			

n: number of patients; %: Column percentage; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HT: Hypertension

Table 4. Distribution of renal function test results of all patients at the beginning and end of follow-up

Parameter	n	Baseline	Final	p*
		mean±SD (min-max)	mean±SD (min-max)	
Urea (mg/dL)	59	60.8±50.9 (17-234)	65.8±52.2 (13-268)	0.268
Creatinine (mg/dL)	59	1.9±1.8 (0.6-9.0)	2.2±2.2 (0.6-9.1)	**0.025**
e-GFR (ml/min)	59	64.6±38.1 (5-125)	61.3±38.0 (5-123)	**0.034**
Proteinuria (mg/gr)	48	1419.9±1973.3 (34-7894)	1488.2±2009.3 (34-8116)	0.151

n: number of patients; SD: Standard deviation; * Wilcoxon Signed Ranks Test

Study groups were homogenous in terms of age, gender, BMI, DM, smoking status, follow-up period and antihypertensive medications (p> 0.05).

The distribution of 24-hour ABPM measurements with respect to SBP-CV quartiles is presented in Table 5. Daytime, night and total DBP values in the first quartile were significantly higher than the other quartiles (p = 0.014; p = 0.012; p = 0.013, respectively (Table 5).

A statistically significant difference was found between the study groups determined according to SBP-CV in terms of daytime, night and total DBP-CV values (p <0.001; p = 0.001; p <0.001, respectively). As a result of the post-hoc comparisons, it was found that the significant difference in daytime DBP-CV was due to the first quartile, and the significant differences in night and total DBP-CV were between the 1st quartile and the 3rd and 4th quartiles. According to SBP-CV, the daytime DBP-CV value of the patients in the first quartile was significantly lower than the other quartiles, while the night and total DBP-CV values were significantly lower than the 3rd and 4th quartiles (Table 5).

Table 5. The distribution of 24-hour ambulatory blood pressure measurements with respect to SBP-CV quartiles

Parameter	1st Quartile (n=15)	2nd Quartile (n=15)	3rd Quartile (n=14)	4th Quartile (n=15)	p[x]
DBP-Daytime	93.3±11.3 (76-110)[bcd]	79.6±11.2 (65-103)	79.9±10.7 (59-105)	84.8±16.0 (50-104)	**0.014**
DBP-CV-Daytime	10.8±2.7 (5.7-16.9)[bcd]	13.4±3.0 (7.8-21.9)	14.9±4.2 (11.2-26.1)	16.2±3.2 (12.5-22.6)	**<0.001**
DBP-Night	88.7±14.4 (67-109)[bcd]	72.1±15.7 (67-109)	71.1±11.1 (52-89)	75.8±17.1 (45-101)	**0.012**
DBP-CV-Night	9.7±2.8 (5.7-15.8)[cd]	10.9±1.5 (8.6-14.6)	14.8±4.2 (10.0-23.1)	12.9±3.9 (4.1-20.4)	**0.001**
DBP-Total	92.3±11.9 (75-109)[bcd]	78.1±12.2 (63-103)	77.7±10.2 (58-101)	83.1±16.4 (49-104)	**0.013**
DBP-CV-Total	11.0±2.5 (7.1-15.8)[cd]	14.1±2.8 (8.8-20.8)	16.0±3.7 (12.5-25.7)	16.4±2.8 (13.3-21.4)	**<0.001**
Systolic Non-Dipper	12 (80.0)	9 (60.0)	10 (71.4)	8 (53.3)	0.422[y]
Diastolic Non-Dipper	11 (73.3)	7 (46.7)	7 (50.0)	5 (33.3)	0.173[y]
Systolic/Diastolic Non-Dipper	9 (60.0)	7 (46.7)	6 (42.9)	5 (33.3)	0.530[y]

n: number of patients; %: Column percentage; SD: Standard deviation; BMI: Body mass index; CKD: Chronic kidney disease; DM: Diabetes mellitus; Continuous variables "mean±standard deviation (minimum-maximum)". categorical variables are presented as "number of patients (column percentage)"; [x]Kruskal Wallis Test; [y]Chi-SquareTest

In addition to SBP-CV, 59 patients were also divided into 4 study groups according to the DBP-CV values. A statistically significant difference was found between the study groups that were determined according to DBP-CV in terms of age, gender and smoking status (p=0.009; p=0.015; p=0.025, respectively). As a result of the post-hoc comparisons, it was found that the significant difference in age was between the 1st quartile and the 2nd quartile. The age of those in the first quartile was significantly lower than those in the second quartile. Furthermore, while the percentage of men in the 1st quartile was significantly higher than the other quartiles, the percentage of smokers in the 4th quartile was significantly lower than the other quartiles. On the other hand, there was no statistically significant difference between the study groups determined according to DBP-CV in terms of BMI value, presence of DM, follow-up period, the use of antihypertensive CCB, beta-blocker, diuretic, ARB, ACEI and alpha-blocker and the number of antihypertensive medications (p > 0.05).

A statistically significant difference was found between the study groups that were determined according to DBP-CV in terms of total SBP value (p=0.018). As a result of the post-hoc comparisons, it was found that the significant difference was between the 4th quartile and the 1st and 2nd quartiles. According to DBP-CV, the total SBP value of the patients in the 4th quartile was significantly lower than the 1st and 2nd quartiles. Regarding the coefficients of variation; a statistically significant difference was found between the study groups determined according to DBP-CV in terms of daytime, night and total SBP-CV values (p <0.001; p = 0.009; p <0.001, respectively). As a result of the post-hoc comparisons, it was found that the significant differences in daytime and total SBP-CV was due to the 1st quartile, and the significant difference in night SBP-CV was between the 1st quartile and the 4th quartile. According to DBP-CV, the daytime and total SBP-CV values of the patients in the first quartile were significantly lower than the other quartiles, while the night SBP-CV values were significantly lower than the 4th quartiles. In addition, a statistically significant difference was found between the study groups that were determined according to DBP-CV in terms of diastolic dipping status and systolic/diastolic dipping status (p <0.001 for both). The percentage of diastolic and systolic/diastolic non-dippers among those in the first and second quartiles was significantly higher than in the third and fourth quartiles. On the other hand, no statistically significant difference was found between the study groups determined according to DBP-CV in terms of daytime and night SBP values and systolic dipping status (p> 0.05).

The relation between the study groups determined according to DBP-CV and the change in e-GFR over time is presented in (Table 6).

A statistically significant difference was found between the study groups determined according to DBP-CV in terms of the reduction amount of e-GFR at the end of the follow-up period compared to the beginning (p = 0.028). As a result of the post-hoc comparisons, a significant difference was found between the 1st quartile and the 3rd quartile. The reduction amount of e-GFR of the patients in the first quartile was significantly lower than those in the third quartile (Table 6). On the other hand, no statistically significant difference was found between the study groups determined according to DBP-CV regarding rapid progression (p = 0.168) (Table 6).

Table 6. The change in e-GFR values over time with respect to DBP-CV quartiles

Parameter	1st Quartile (n=15)	2nd Quartile (n=15)	3rd Quartile (n=14)	4th Quartile (n=15)	p[x]
The amount of decrease in e-GFR, ml/min/year	0.7±8.1 (-14-18)[c]	3.9±21.6 (-9-81)	6.6±7.4 (0-20)	2.1±5.5 (-9-14)	**0.028[x]**
Patients with rapid progression, n(%)	4 (26.7)	1 (6.7)	6 (42.9)	4 (26.7)	0.168[y]

n: number of patients; %: Column percentage; mean: mean; SD: Standard deviation; BMI: Body mass index; CKD: Chronic kidney disease; DM: Diabetes mellitus; Continuous variables "mean ± standard deviation (minimum-maximum)". categorical variables are presented as "number of patients" (column percentage); [x]Kruskal Wallis Test; [y]Chi-SquareTest

Among 59 patients who were included in the study, 15 (25.4%) patients had rapid progression. No statistically significant difference was found between the patients with rapid progression and those with natural progression regarding age, gender, BMI, presence of DM, smoking status, follow-up period, use of antihypertensive ACEI, ARB, beta blocker, CCB and alpha blocker medication and the number of used antihypertensive medications (p> 0.05). The distribution of renal function test results at the beginning and end of the follow-up period in patients with rapid progression and patients with natural progression is presented in Table 7. The urea and creatinine increased significantly at the end of the follow-up compared to the baseline among patients with rapid progression, while the e-GFR decreased significantly (p = 0.013; p = 0.001; p = 0.001, respectively). On the other hand, no significant change was found in urea, creatinine and e-GFR values at the end of the follow-up compared to the beginning in patients with natural progression (p> 0.05). With regard to the proteinuria, no statistically significant change was found at the end of follow-up compared to the beginning in both patients with rapid progression and natural progression (p> 0.05) (Table 7).

Table 7. Distribution of renal function test results at the beginning and end of the follow-up in patients with rapid progression and natural progression

Parameter		n	Rapid Progression mean±SD (min-max)	n	Natural Progression mean±SD (min-max)	p**
Urea (mg/dL)	Baseline	15	46.8±28.6 (17-126)	44	65.6±56.0 (18-234)	0.304
	Final	15	63.6±42.4 (21-152)	44	66.6±55.6 (13-268)	0.801
	p*		**0.013**		0.695	
Creatinine (mg/dL)	Baseline	15	1.5±1.1 (0.7-4.4)	44	2.0±2.0 (0.6-9.0)	0.503
	Final	15	2.5±2.4 (0.7-8.9)	44	2.1±2.1 (0.6-9.1)	0.519
	p*		**0.001**		0.922	
e-GFH (ml/min)	Baseline	15	73.6±38.2 (13-125)	44	61.5±38.0 (5-123)	0.236
	Final	15	57.5±38.3 (6-105)	44	62.6±38.3 (5-123)	0.657
	p*		**0.001**		0.181	
Proteinuria (mg/gr)	Baseline	12	907.7±1125.5 (34-3163)	36	1590.7±2170.4 (54-7894)	0.199
	Final	12	1039.8±1291.1 (34-3365)	36	1637.8±2192.2 (54-8116)	0.432
	p*		0.345		0.259	

n: number of patients; SD: Standard deviation; * Wilcoxon Signed Ranks Test; **Mann-Whitney U Test

No significant difference was found between patients with rapid progression and those with natural progression regarding daytime, night and total SBP, SBP-CV, DBP and DBP-CV values (p> 0.05).

The independent effect of SKB-CV in predicting rapid progression was investigated by controlling different variables. Accordingly, SBP-CV was found to have no effect on prediction of rapid progression (p> 0.05). Likewise, the independent effect of DBP-CV on prediction of rapid progression was investigated by controlling different variables. According to this, DBP-CV was found to have no effect in predicting rapid progression (p> 0.05).

Discussion

As a result, we did not detect any significant association between blood pressure variability and renal progression in patients with CKD and HT. Current guidelines recommend that 24-hour ambulatory BP measurements should be used more frequently for diagnosis and monitoring of the treatment effectiveness in high-risk hypertensive populations such as CKD, and even if possible, to be applied to every patient. Although the mean number of antihypertensive medications of the patients was 2.0 ± 0.9, we found that 40.6% of patients had uncontrolled HT. Since 24-hour ambulatory BP measurement (ABPM) cannot be performed on every patient in routine practice in our clinic, these patients were selected as a result of the suspicion of resistant and/or uncontrolled HT being the most important ABP indication, and our study population being obese (mean BMI: 30.9 ± 6.2 kg/m2) and possible dietary and/or drug incompatibility may also have contributed to this situation.

Non-dipper HT pattern, which is defined as no drop more than 10% in blood pressure at night compared to daytime, is an indicator for poor prognosis that leads to increased morbidity and mortality by causing rapid end-organ damage (Davidson, et al. 2006: 846). It is known that the non-dipper HT pattern is more common in CKD patients. The presence of non-dipper HT has been demonstrated to cause increase in cardiovascular events, but the relation between non-dipper HT and CKD progression is unclear. Although it is known that the prevalence of non-dipper HT increases with the progressive decrease in GFR, cross-sectional studies have shown that even the presence of minimal degrees of proteinuria is associated with profound disturbances in circadian rhythms. At any stage of CKD, those with higher proteinuria have less dipping. With regard to the proteinuria, the relation of CKD with the non-dipping pattern is significantly weakened. Although some studies in the literature detected that the presence of non-dipper HT accelerates the progression of CKD, most of these studies did not control the presence of proteinuria, which is an independent risk factor for both CKD progression and the development of non-dipper HT (Gondo, et al. 2015: 545; Höcht, 2013: Article ID 398485). Exceptionally, in a cohort study of 436 CKD patients conducted by Minutolo et al. in 2011, non-dipper HT was demonstrated to be an important risk factor for CKD progression, leading to ESRF, and cardiovascular events, despite 24-hour ABPM, proteinuria, cardiovascular history and other risk factors were adjusted (Minutolo, et al. 2011: 1090). We determined that non-dipper HT pattern was common (45.8%) in our patients. We think that the presence of severe proteinuria (1419.9 ± 1973.3 mg/gr) in our patients may be the reason for the high frequency of non-dipper HT. However, in our study, we did not find a significant relation between non-dipper HT pattern and rapid renal progression. This result is consistent with the suggestion that the presence of non-dipper HT may be a result or a sign of the pathological process that causes rapid renal progression rather than a cause of CKD progression.

Among the studies, there are significant differences in methods and parameters such as type of BP variability (systolic, diastolic), period (short, medium and long term),

measurement method (intra-arterial measurement, 24-hour ABPM, home measurements, visit-to-visit measurements). Also, variables such as age, gender, type of antihypertensive medication, and previous cardiovascular events, which are known to affect the variability of BP, differ among the populations in these studies. Benetos et al. demonstrated a serious relation between increased age and BP variability in their study (Benetos, et al. 2011: 646). Di Iorio et al also showed that increased systolic and diastolic blood pressure variability is associated with increasing age (Di Iorio, et al. 2012: 4404). In our study, we measured the daily (24-hour) BP variability of the patients with 24-hour ABPM. The participants in our study were relatively young patients (mean age: 54.2 ± 14.6 years) with almost equal female-male ratio (50.8% male). There was no statistically significant difference between the study groups determined according to SBP-CV in terms of age, gender, BMI value, presence of DM, type and number of antihypertensive medications. However, in DBP-CV groups, we found that the group with the lowest DBP-CV was younger and consisted of more males, which is in accordance with the literature. The treatment with different classes of antihypertensive medication is known to affect the blood pressure variability. It was demonstrated that calcium channel blockers and non-loop diuretics declined the variability and other antihypertensive classes (especially ACE inhibitors) increased the variability (Webb, et al. 2010: 906). In our study, the most frequently used antihypertensive drug group was calcium channel blockers (CCB) with 57.6%, while the least used antihypertensive drugs were ACE inhibitors (ACEIs) with 22% and alpha-blockers with 15.3%. There was no difference between the groups regarding the type of antihypertensive medication. In a cross-sectional study by Tatasciore et al., a strong relation was found between awake SBP variability and the presence of microalbuminuria (Tatasciore, et al. 2007: 325). In contrast to this study, we did not find a significant relation between proteinuria and BP variability in our study. The low number of patients participating in our study may be a reason for this.

Although there is currently an awareness of BP variability, the relation of this variability with clinical outcomes has not been considered significant historically. The hypertension guideline published by the European Society of Hypertension (ESH) / European Society of Cardiology (ESC) in 2013 did not specify the importance of BP variability in terms of end-organ damage and its management. Current literature mostly indicates that the increase in BP variability is associated with end-organ damage. In the Ohasama observational study by Kikuya M. et al., increased day-to-day BP variability in hypertensive Japanese patients was found to be an independent risk factor for cardiovascular events and stroke (Kikuya, et al. 2008: 1045). Hastie et al., showed that the increase in systolic BP variability was associated with a 60% increased risk of all-cause death in the first year of treatment in 14522 moderately hypertensive patients (Hastie, et al. 2013: 698). Various studies investigating the relation between blood pressure variability and renal survival had provided evidence that increased variability is associated with worsening of renal function. In a recent retrospective study involving approximately 3 million people with an estimated GFR ≥ 60 mL/min/1.73 m^2, increased SBP variability in individuals with and without HT was found to be associated with a significantly increased risk of developing all-cause death, heart failure, stroke, and ESRF (Gosmanova, et al. 2016: 1375). Post-hoc analysis of the RENAAL and ALLHAT studies showed that increased systolic BP variability is an independent risk factor for the development of CKD and ESRF (McMullan, et al. 2014: 714; Whittle, et al. 2016: 471). At the same time, unlike the variability of BP from visit to visit, there is less evidence about the relation between daily BP variability obtained with 24-hour ABPM and renal survival. Also contrary to the general opinion in the literature, there are also studies with different results. In the study of Sahutoglu T. that was conducted in Turkey, increased DBP variability in the 24-hour ambulatory measurements of the CKD patients was found to be associated with better renal outcomes and increase in DBP variability may be a good prognostic factor in CKD patients (Sahutoglu-Sakaci, 2018: 46). Although we have found a significant decrease in the annual amount of e-GFR decrease in the group with the lowest DBP variability, we could not find a significant relation between systolic and diastolic BP variability and rapid renal progression development in CKD patients. In the regression analysis performed by controlling parameters such as age, gender, presence of DM, initial e-GFR value and dipping status, we found that systolic and diastolic BP variability had no independent effect on predicting rapid renal progression. Similar to our study, the effect of 24-hour systolic and diastolic BP variability on CKD progression was investigated in a study conducted by Manios et al. in which 803 hypertensive patients without treatment were included, and no significant relation was found (Manios, et al. 2009: 2244). Another similar study, Di Iorio et al. conducted a multicenter study with 374 CKD patients with e-GFR <60 mL/min/1.73m^2, and found that all-cause mortality increased as systolic BP variability increased, and systolic BP variability may be an independent marker of mortality in these patients however no relation was detected between BP variability and CKD progression (Di Iorio, et al. 2012: 4404). We think that such contradictory results in the literature may be due to differences in patient selection, material method and design. Nevertheless, physical activity, which is an important parameter that may affect BP variability, cannot be measured in studies and this may be an important limitation. More detailed large-scale studies in which the physical activity of the patients is also followed in addition to 24-hour ABPM should be conducted about this subject. Also, prospective studies are needed to evaluate whether blood pressure variability should be considered as a therapeutic goal in the management of antihypertensive treatment of CKD patients.

The fact that it is a retrospective and observational study, the number of patients and the duration of follow-up are low, 24 ABPM was applied to the patients only once at the beginning of the study (control ABS was not performed), and the physical activities of the patients were not recorded during ABS.

Conclusion

Uncontrolled and non-dipper HT is a common problem in CKD patients. The presence of uncontrolled HT is one of the most important risk factors for rapid renal progression and end stage renal failure. There was no significant relation between blood pressure variability and rapid renal progression.

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