Original Paper

In Patients with Chronic Kidney Disease Short Term Blood Pressure Variability is Associated with the Presence and Severity of Sleep Disorders

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Key Words

Blood pressure variability • CKD • Insomnia • Sleep quality • Restless legs syndrome

Abstract

Background/Aims: In chronic kidney disease (CKD) patients blood pressure variability (BPV) is associated with poor outcome. Sleep disturbances alter BP profiles in hypertensives but their influence on BPV in CKD patients is unknown. We screened a cohort of CKD/ESRD patients to investigate whether sleep quality impacts on BPV. **Methods:** Consecutive CKD patients' sleep quality was assessed using validated questionnaires (Epworth Sleepiness Scale-ESS; International Restless legs scale-IRLS; Functional Outcomes of Sleep Questionnaire-FOSQ; Insomnia Severity Index-ISI; STOP-Bang). All patients underwent ambulatory blood pressure measurement. **Results:** 104 out of 143 enrolled patients (78.32% stage-3 CKD; 10.49% Stage-4; 11.19% Stage-5; 6.99% ESRD-under dialysis) completed all the questionnaires. 95.8% were hypertensives, 70% were non-dippers and 27.8% had resistant hypertension. STOP-Bang >4 proved sleep disorders in 84.84% of patients. Patients with IRLS >10 had greater diastolic nocturnal standard deviation (DNSD) and a trend ($p=0.05$) for systolic nocturnal SD (SNSD). Patients with ISI >14 had greater SNSD and in 28.8% FOSQ showed severely impaired sleep quality. Their systolic nocturnal BPV was significantly greater. ISI was independently associated with SNSD. FOSQ and diastolic nocturnal BPV were negatively correlated at the bivariate analysis and FOSQ independently predicts systolic nocturnal BPV at multivariate regression analysis. **Conclusions:** In CKD patients impaired sleep quality increases BPV, might contribute to their disease progression and worsen prognosis. Searching for sleep problems in CKD patients could help planning their treatment of sleep problems contributing to CV risk reduction. Our data provide the rationale working hypothesis for the need of studies with

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larger number of patients aimed to demonstrate improved outcome of CKD progression and CV risk with the treatment also of sleep disorders.

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Introduction

Elevated absolute blood pressure (BP) values are not the only causes of adverse cardiovascular (CV) consequences of hypertension. BP variability (BPV) has been demonstrated to closely relate with target organ damage and to be a significant predictor of mortality, CV events and stroke [1-3].

BPV is defined as the fluctuations of blood pressure values between different measurements over a defined time interval [4] and is influenced by behavioural, environmental, humoral factors and neural central, and reflex stimuli [5].

BP fluctuations can be assessed over different time intervals: in the very short term with a beat-to-beat monitor, in the short term with a 24-h ambulatory BP monitoring (ABPM) and in the long term with day by day measurements [4]. In particular, short term BPV can be estimated through the standard deviations (SD) of the average systolic and diastolic arterial pressure values over the 24h, daytime, and night-time period [5].

Among these different short term BPV parameters, none is still considered to be the most representative of "true" BPV. However, nocturnal BPV has been associated with increased risk of CV events, CV mortality, and all-cause mortality among patients with hypertension even when accounting for several risk factors and other potential confounders, including average night-time BP [6]. This is not unexpected as nocturnal BPV is less affected by occasional triggers, better reflecting pathophysiological conditions such as baroreflex dysfunction or arterial stiffness.

Moreover, despite the increasing evidence for a correlation between short term BPV and the development, progression and severity of cardiac, vascular and renal organ damage [7], the effect of different antihypertensive drugs on short term BPV is still unclear [8, 9].

In patients with chronic kidney disease (CKD) the role of BPV is still under debate. Although no study has demonstrated that BPV is superior to absolute BP to predict the progression of renal disease, there is evidence that BPV negatively correlates with glomerular filtration rate [7].

The prevalence of sleep disorders, such as obstructive sleep apnoea (OSA) [10], restless legs syndrome (RLS) [11] and sleep insomnia [12] is higher in patients with CKD. Moreover, there is evidence that RLS may enhance mortality in patients with end-stage CKD [13].

The aim of the present study was to investigate the relationship between BPV and kidney function, and to analyse the changes in short term nocturnal BPV parameters in relation to different sleep disorders such as RLS, sleep insomnia and sleep apnoea in a cohort of patients with CKD.

Materials and Methods

Consecutive patients were assessed between January 2014 and January 2017 in our outpatient Nephrology and Hypertension clinic at the Department of Medicine, University of Padova, Italy.

We included patients aged ≥ 18 years, either males or females with chronic kidney disease defined by a estimated glomerular filtration rate (eGFR) ≤ 60 ml/min/1.73m². Patients with acute illness or pregnancy were excluded.

Patient underwent a baseline clinical assessment, which included demographics, past medical history and current treatment. Office BP, neck circumference, height, and weight were assessed, and body mass index (BMI) was calculated.

Patients underwent blood tests measuring urea and creatinine, also eGFR was calculated with the defined per MDRD formula [14].

Assessment of blood pressure variability

All patients underwent 24 h ambulatory blood pressure monitoring (24 h ABPM) using validated devices (Spacelabs 90207; SpaceLabs™, Washington, USA). The between measurement intervals were 15 min (daytime) and 20 min (night-time). During each recording, subjects were required to attend at their usual daily activities, only refraining from unusual physical exercise or behavioural challenges. Patients were also asked to mark on a diary their main activities, including the time of meals, bed rest or sleep, and awakening times. Only recordings rated as of sufficient quality, i.e. including at least 70% of valid readings over the 24-h and at least two valid readings per hour during daytime and one valid reading per hour during night-time, were considered for the final analysis. Day and night periods were defined and corrected according to what reported by the patient in the diary. The average daytime period is identified as the interval from 0800 h to 2300 h and the night period as the interval from 2300 h to 0800 h. All procedures were done according to current guidelines [15, 16].

From each recording we have calculated: the average 24-h, day and night systolic (SBP) and diastolic (DBP) blood pressure; the degree of nocturnal BP fall and the standard deviations (SD) of the mean of all individual readings over the different time periods considered.

Based on the degree of nocturnal BP fall, subjects were classified as dippers (BP fall $\geq 10\%$ and $<20\%$ of daytime average BP), non-dippers (fall $<10\%$), and extreme dippers (BP fall $\geq 20\%$) [16].

Assessment of sleep quality and sleep disorders

We administered 5 validated questionnaires in order to evaluate the presence/absence and severity of sleep disorders and to assess the patient's sleep quality.

Epworth Sleepiness Scale (ESS) to assess excessive daytime sleepiness. It is a self-administered questionnaire with 8 items. Respondents are asked to rate, on a 4-point scale (0-3), their usual chances of dozing off or falling asleep while engaged in eight different activities [17]. An ESS > 10 points suggests the presence of excessive daytime sleepiness.

International Restless Legs Scale (IRLS). A 10 items questionnaire which assesses the presence of symptoms of RLS and the impact of the sleep disorder on quality of life [18]. Diagnosis of the severity of RLS is done through a series of 10 questions, each scores using a RLS rating of 0 to 4 and therefore leading to a maximum total score of 40. The severity of RLS symptoms are scored as: mild (total score of 1-10), moderate (11-20), severe (21-30), very severe (31-40).

Functional Outcomes of Sleep Questionnaire (FOSQ). It is a 30 items questionnaire assess the impact of disorders of excessive sleepiness on multiple activities of everyday living and the extent to which these abilities are improved by effective treatment [19]. Scaling of items goes from 0 to 4 or 0 to 6. The total score ranges from 5 to 20 and a score of more than 17.9 is used as the threshold for defining a normal sleep-related quality of life [20].

Insomnia Severity Index (ISI). Designed as a brief screening tool for insomnia, the seven-item questionnaire asks respondents to rate the nature and symptoms of their insomnia problems such as the respondent's satisfaction with his or her sleep patterns and the degree to which insomnia interferes with daily functioning [21]. A 5-point Likert scale is used to rate each item (e.g., 0 = no problem; 4 = very severe problem), yielding a total score ranging from 0 to 28. The total score is interpreted as follows: absence of insomnia (0-7); sub-threshold insomnia (8-14); moderate insomnia (15-21); and severe insomnia (22-28).

STOP-Bang questionnaire. A 8 items questionnaire developed in response to the need for a concise, user-friendly OSA screening tool in preoperative clinics, now it is considered concise, effective, and reliable resource in both diagnosing and treating previously unrecognized OSA. It includes four questions related to snoring, tiredness, observed apnoea and high blood pressure, plus four additional demographic queries (BMI, age, neck circumference and male gender). Questionnaire interpretation as follows: score of 0-2: low risk, score 3-4: intermediate risk, score >4 : high risk [22]. A score of >4 has been found to have a sensitivity of 88% for OSA [23].

Statistical analysis

Statistical analyses were performed using GraphPad Prism® (version 7.03, GraphPad Software Inc, San Diego, CA, USA) and SPSS Software® (Version 20, IBM, Chicago, IL, USA).

Table 1. Main characteristics of the total sample of patients enrolled and of the subgroup of patients with all 5 sleep questionnaires completed. COPD=Chronic Obstructive Lung Disease

	Enrolled patients (n = 143)	Subgroup with questionnaires completed (n = 104)	p =
Males (n,%)	76 (53%)	M 57 (54.81%)	0.796
Age (years)	71 (28-94)	71.5 (65-78.7)	0.892
BMI (kg/m ²)	26.7 (15.8-43.7)	26.8 (23.6 - 29.9)	0.954
Urea levels (mmol/l)	9.4 (3.4-53.7)	9.4 (7.3-14.9)	0.862
Creatinine (μmol/l)	128 (78-1128)	130.5 (107-180)	0.925
eGFR (ml/min/1.73m ²)	44.8 (3-60)	44.7 (32.2 - 52)	0.941
Stage 3 CKD (n, %)	112 (78.32%)	80 (76.7 %)	0.7942
Stage 4 CKD (n, %)	15 (10.49%)	12 (11.65 %)	0.7942
Stage 5 CKD (n, %)	16 (11.19%)	11 (10.68 %)	0.8791
Patients on dialysis (n, %)	10 (6.99%)	8 (7.69 %)	0.835
Medical history			
Arterial hypertension (n, %)	137 (95.8%)	102 (99 %)	0.025
Resistant hypertension (n,%)	39 (27.27 %)	29 (27.8 %)	0.915
Diabetes (n, %)	26 (18.18%)	18 (17.31 %)	0.859
Obstructive sleep apnoea (n, %)	8 (5.59%)	5 (4.81 %)	0.785
Atrial fibrillation (n, %)	18 (12.59%)	14 (13.46 %)	0.840
Hypothyroidism (n, %)	12 (8.39%)	8 (7.69%)	0.842
COPD (n, %)	18 (12.59%)	14 (13.46 %)	0.840
Antihypertensive medications			
Calcium channel antagonists (n, %)	77 (53.8%)	56 (53.85 %)	1.000
Beta blockers (n, %)	71 (49.65%)	55 (52.88 %)	0.616
Angiotensin-converting enzyme (ACE) Inhibitors (n, %)	41 (28.67%)	28 (26.92 %)	0.762
Angiotensin receptor blockers (ARBs) (n, %)	65 (45.45%)	52 (50 %)	0.480
Diuretics (n, %)	81 (56.64%)	61 (58.65 %)	0.752
Minerakortocoid antagonists (n, %)	11 (7.69%)	7 (6.73 %)	0.774
Nitrates (n, %)	6 (4.2%)	5 (4.81 %)	0.818
Alfa-blockers (n, %)	30 (20.98%)	24 (23.08 %)	0.694

Descriptive statistics were performed to calculate percentages, mean, median, and standard deviation. Normality was assessed with D'Agostino-Pearson test. Non normal variables were expressed as median and interquartile ranges whilst normal variable with mean and standard deviation. Comparison of BPV among patients with different scoring in the sleep questionnaires was performed with Mann-Whitney test.

We conducted bivariate analysis performing Spearman test for non normal variables and Pearson test for normally distributed variables to assess the correlation between BPV and sleep questionnaires scoring. Multiple regression was also performed for nocturnal BPV as dependent variable. $p < 0.05$ was considered as significant.

Results

A total of 143 patients were enrolled, 39 of which could not complete all the 5 sleep questionnaires. Main characteristics are summarised in Table 1; more than half of patients were males, BMI was in the overweight range (26.7 (15.8-43.7) kg/m²). Most of the patients had stage 3 CKD and eGFR was on average 44.8 (3-52) ml/min/1.73 m². With regards to the medical history almost all of them had arterial hypertension (95.8%) and about 27% with resistant hypertension, defined as BP > 140/90 mmHg despite treatment with ≥ 3 antihypertensive agents, including diuretics. Only 18.18% had diabetes.

The majority of patients (56.64%) were on diuretics and only 7.69% were on mineralcorticoid antagonists.

Blood pressure and blood pressure variability parameters are shown in Table 2. Average systolic and diastolic blood pressure in the 24 hours were 138.3 (126.15-150.45) and 74 (53-105) respectively. One third of patients exhibited a dipping pattern of nocturnal blood pressure thus the remaining two thirds had an abnormal blood pressure profile at night.

Sleep disorders were frequent in this cohort of subjects: STOP Bang questionnaire was greater than 4 points in 84.84% of the subjects suggesting a high prevalence of sleep-disordered breathing. Excessive daytime sleepiness was not so common amongst patients with a number of subjects scoring >10 at the ESS of 2.88%. 32.69% of patients had moderate-severe symptoms of RLS and less than 10% of subjects had features of insomnia (Table 3). Overall sleep-related quality of life was impaired in almost one third of participants although median adjusted FOSQ was 19 (17.7-19.7).

Table 2. BP and BPV parameters. Normally distributed variable

	Enrolled patients (n = 143)	Subgroup with questionnaires completed (n = 104)	p =
SBP 24 h (mmHg) [#]	134.3 (15.15)	133.6 (15.29)	0.734
DBP 24 h (mmHg)	74 (53-105)	73 (66-79)	0.666
Systolic SD 24 h (mmHg)	13 (7-28)	13 (11-17)	0.939
Diastolic SD 24 h (mmHg) [#]	9.9 (2.6)	9.9 (2.62)	0.826
SBP day (mmHg) [#]	137.1 (15.31)	136.5 (15.51)	0.789
DBP day (mmHg)	76 (53-109)	76 (69-83)	0.709
Systolic SD day (mmHg)	12 (6-27)	12 (10-15)	0.921
Diastolic SD day (mmHg)	8 (4-17)	8 (7-10)	0.944
SBP night (mmHg)	125 (88-186)	124 (116-138)	0.683
DBP night (mmHg)	64 (45-103)	66 (59-74)	0.684
Systolic SD night (mmHg)	10 (5-23)	10 (8-13)	0.681
Diastolic SD night (mmHg) [#]	8.17 (2.61)	7.92 (2.73)	0.535
Dippers (n,%)	46 (32.17%)	37 (35.58%)	0.576
Non dippers (n,%)	36 (25.17%)	30 (28.85%)	0.520
Reverse dippers (n,%)	15 (10.49%)	9 (8.65%)	0.631
Dipping not available (n,%)	28 (19.58%)	28 (26.92%)	0.174
Dipping (mmHg)	6.7 (-32.9 – 24.1)	7.2 (2.42-12.7)	0.619

Table 3. Results of the sleep questionnaires administered for the subgroup of 104 patients. FOSQ = Functional Outcomes of Sleep Questionnaire, aFOSQ = adjusted FOSQ, ESS = Epworth Sleepiness Scale, IRLS = International Restless Legs Scale, ISI = Insomnia Severity Index

Subgroup with questionnaires completed (n = 104)	
ESS (points)	4 (0-18)
patients with ESS > 10 (n,%)	3 (2.88)
IRLS (points)	8 (0-28)
patients with IRLS > 10 (n,%)	34 (32.69)
patients with IRLS ≥ 1 (n,%)	72 (69)
FOSQ (points)	97 (76.7-106.2)
aFOSQ (points)	19 (17.7-19.7)
patients with aFOSQ < 17.9 (n,%)	30 (28.8)
ISI (points)	5 (0-18)
patients with ISI > 14 (n,%)	10 (9.61)
patients with ISI > 7 (n,%)	48 (46)
STOP Bang > 4 (n,%)	84 (84.84)

Fig. 2. Significantly Increased systolic nighttime SD in CKD patients with ISI > 14.

Fig. 1. Significantly Increased diastolic nighttime SD in CKD patients with IRLS > 10.

Fig. 3. Significantly Increased systolic nighttime SD in CKD patients with an adjusted FOSQ < 17.9 points.

Table 4. Analysis of the 5 FOSQ domains. FOSQ = Functional Outcomes of Sleep Questionnaire

NOCTURNAL BPV						
FOSQ domains	SYSTOLIC			DIASTOLIC		
	>3.58	<3.58	P value	>3.58	<3.58	p =
General Productivity	9.78	12.17	0.001	7.75	8.37	0.276
Social Outcome	10.16	11.84	0.061	7.76	8.53	0.392
Activity level	9.57	11.8	0.001	7.52	8.48	0.080
Vigilance	10.16	11.84	0.017	7.91	8.11	0.651
Intimacy and Sexual Relationships	9.45	11.48	0.003	7.52	8.31	0.206

When comparing BPV variables with the different questionnaires we found no differences when comparing patients at high risk of OSA (STOP Bang > 4) with patients with STOP Bang < 4.

Patients with IRLS>10 exhibited a greater diastolic nocturnal SD (8 [7-11] vs 7 [5-9], $p=0.0161$ (Fig. 1), whilst there was a strong tendency toward an increased systolic nocturnal SD, (11 [9-14] vs 10 [8-12], $p=0.05$).

We did find that patients with ISI > 14 had a greater systolic nocturnal SD (13 [11-15.5] vs 10 [8-12], $p=0.0189$ (Fig. 2). No differences were found with regards to diastolic nocturnal SD.

No differences in terms of systolic and diastolic nocturnal SD in patients with and without excessive daytime sleepiness. However, in patients with impaired sleep-related quality of life as expressed by an adjusted FOSQ<17.9 points, nocturnal systolic BPV was greater (12.73 vs 9.71, $p < 0.0001$, (Fig. 3). When we considered singularly each FOSQ domain we found that systolic BPV was increased in all domains except social outcomes. No significant differences were found for diastolic BPV (Table 4).

Bivariate and multivariate analysis

A significant negative correlation was found with all systolic blood pressures and eGFR (SBP 24 h - 0.4021, SBP day - 0.4185, SBP night - 0.3235, $p < 0.0001$). Although weak, a negative correlation was found also between eGFR and nocturnal DBP (- 0.1709, $p < 0.05$). No significant correlation was found with BPV parameters. A multiple regression (Table 5) confirmed that ISI was associated with systolic nocturnal SD independently from sex, BMI, eGFR and systolic

Table 5. Multiple regression with systolic nocturnal BPV as dependent variable and age, sex, BMI, ISI, eGFR and systolic nocturnal BP as covariates

Model	Unstandardised Coefficients		t	p =
	B	Std. Error	β	
1 (Constant)	3.161	4.166	.759	.450
age	.075	.026	.275	2.854 .005
sex	-.027	.669	-.004	-.040 .968
BMI	.086	.063	.130	1.363 .176
ISI	.189	.067	.280	2.828 .006
GFR	-.014	.023	-.066	-.627 .532
SBPnight	-.006	.020	-.028	-.279 .781

Table 6. Multiple regression with systolic nocturnal BPV as dependent variable and age, sex, BMI, aFOSQ, eGFR and systolic nocturnal BP as covariates

Model	Unstandardized Coefficients		Standardized Coefficients	t	p =
	B	Std. Error	β		
1 (Constant)	13.548	4.918		2.755	.007
age	.055	.028	.202	1.975	.051
sex	-.155	.670	-.022	-.231	.818
BMI	.067	.063	.101	1.052	.295
GFR	-.009	.024	-.043	-.394	.695
SBPnight	-.011	.020	-.058	-.568	.571
aFOSQ	-.359	.149	-.257	-2.412	.018

nocturnal BP ($\beta = 0.280$, $p < 0.05$), but dependently from age ($\beta = 0.275$, $p < 0.05$). The bivariate analysis between IRLS and diastolic nocturnal BPV did not show any significant correlation whilst between FOSQ and diastolic nocturnal BPV confirmed a negative correlation (-0.336 , $p < 0.001$). The multivariate regression showed that FOSQ predicts systolic nocturnal BPV independently from the main confounders (Table 6).

Discussion

The main findings of the present study are that eGFR is correlated with predominantly diurnal and nocturnal systolic blood pressures but not with short term BPV. We found that in patients with CKD, short term BPV is influenced by the presence of sleep disorders being greater in patients with moderate-severe RLS and insomnia.

The former finding further supports the results of previous studies [24], highlighting again the role of blood pressure in the development of CKD.

We could not confirm that eGFR was associated with neither diurnal nor nocturnal BPV as shown by Tanner and coworkers [25]. They demonstrated that in a large sample of patients with CKD, BPV defined by day-night standard deviation and average real variability, was higher among participants with versus without CKD. Interestingly, these differences were not statistically significant after further multivariable adjustment including 24 h mean systolic blood pressure. This again is not surprising as there are many determinants of BPV such as age other than BP absolute values [26] that makes it difficult to understand if BPV is an independent risk factor for CV disease.

Although in our study BPV was not correlated with renal function, the current evidence shows that BPV, in particular visit-to-visit BPV, is indeed associated with GFR [27] and independently correlates with death and cardiovascular events [28, 29]. Most interestingly, the latter association is independent of mean absolute values of BP [30], again underlining the importance of the variability of blood pressure values over time. However, it is important to note that the time interval considered when calculating BPV, does matter with regards to the association between BPV and various cardiovascular outcomes. For example, when BPV is assessed in a large time range, the association with both CV events and CV mortality is rather strong and significant, whilst if a shorter time range is considered, the association with CV events is less evident [31].

A possible explanation of this phenomenon is that BP fluctuations over short periods of time are more related to alterations of the autonomous nervous system and to other humoral and rheological factors whilst long term visit-to-visit BPV is more associated with arterial compliance or other factors such as adherence and compliance to anti-hypertensive medications [32]. These findings all together should suggest the nephrologist to consider not only absolute BP values, but also BPV during the risk stratification of patients with CKD [33].

The second finding of this study is of particular clinical relevance giving the high prevalence of sleep disorders amongst patients with CKD. It has been reported that 80% of end stage CKD patients under chronic dialysis report sleep complaints, with daytime sleepiness to be the most common reported symptom [34]. The cause of this is presumably multifactorial: sympatho-vagal imbalance due to baroreceptor reflex function impairment and consequent hyperactivity of the sympathetic nervous system and decreased vagal tone [35] but also the decreased nocturnal melatonin levels in patients with CKD [36].

In our study we reported a prevalence of sleep disordered breathing, although estimated through a self-report questionnaire, of 85%. These data are in line with previous studies reporting a prevalence of about 70%-80% of CKD patients even when the diagnosis was based on polysomnography [37].

Studies found an increased nocturnal BPV, when measured with systolic and diastolic SD, in patients with OSA compared with controls [38]. Rather surprisingly, we did not find

any difference with regards to BPV when comparing patients at high and low risk of OSA. This can be explained by the fact that questionnaire based diagnosis does not differentiate the severity of the disease. Furthermore, our study enrolled mainly patients with mild to moderate CKD with less than 10% of patients on dialysis. This is relevant giving that patients with end stage renal disease (ESRD) are more likely to have OSA due to “rostral fluid shift” by which fluid shifts from the legs towards the neck leading to upper airway restriction and collapse [39].

RLS was highly prevalent in our cohort of patients with 32.69% of subjects experiencing moderate to severe symptoms. These data are similar to what has been already shown by Winkelman et al. where in ESRD the prevalence of RLS is 20%-30%, compared to 3%-7% in the general population [40].

In our study, nocturnal BPV was greater in patients with moderate to severe RLS. This is not surprising given the high prevalence in these patients of periodic limb movements at night which can increase arterial stiffness and sympathetic discharge and being responsible of the high BP fluctuations at night [41].

Insomnia is a common sleep disorder in the general population and is significantly more common in CKD and in patients on dialysis [42]. Although the prevalence of patients with clinically significant insomnia was rather low in our study, we found an increased nocturnal systolic BPV when compared with patients with mild symptoms or no insomnia. This novel finding is clinically important as many causes of insomnia in CKD patients can be treated such as pain, one of the most common causes of insomnia [43], but also dialysis shift times which are an important risk factor for the development of insomnia [12].

Thus assessing CKD patients for insomnia and RLS can potentially contribute to a better stratification of patients' CV risk and the treatment of these sleep disorders can potentially improve patients outcome by reducing nocturnal BPV.

With regards to the impact of sleep disorders on daytime sleepiness and on multiple activities of everyday living we found a low prevalence of patients complaining of excessive daytime sleepiness as less than 3% of patients had an ESS >10. This is in contrast with the results of studies by Parker and coworkers [44] where 46 patients underwent polysomnography and multiple sleep latency test other than subjective assessment of daytime sleepiness with ESS. They found that 30% of patients had an ESS >10 suggesting daytime sleepiness. But again those were mostly patients on dialysis in which prevalence of sleep disorders is greater when compared with stable stage 3 CKD patients.

Interestingly, FOSQ predicted nocturnal systolic BPV in our cohort of patients, independently from the main confounders. This suggests that in such patients, sleep disturbances that impact on multiple activities of everyday living can have a detrimental effect on their CV risk.

To the best of our knowledge this is a novel finding and deserves future confirmation in large population based studies in order to understand if FOSQ can also predict mortality and CV events in CKD patients.

Some limitations need to be acknowledged. Firstly, the lack of objective testings with regards to sleep disorders assessment: we used validated questionnaires with proven scoring test-retest reliability and internal consistency as recommended by the American Thoracic Society [45]. In our cohort of patients full polysomnography was unfeasible and the use of questionnaires allowed to recruit a larger sample of patients. Secondly, questionnaires were administered by research fellows or dedicated nurses thus a bias could have potentially yielded inaccurate results [46].

Conclusion

Our study shows that eGFR correlates with absolute blood pressure values but not with BPV, which is a predictor of cardiovascular events and mortality in patients with

CKD. However, we showed that BPV is strongly associated with sleep disturbances such as insomnia and RLS, which are known to worsen quality of life and are associated with higher cardiovascular morbidity. The search for the presence of sleep problems whilst assessing patients with CKD can help diagnosing patients at even higher risk and most importantly could help planning a treatment with the aim of not only treat the underlining sleep disorder but also to contribute to the reduction of the patient's CV risk. More prospective studies with larger number of patients are needed to confirm these findings and to demonstrate that the treatment of sleep disorders can improve outcomes in CKD patients. The data coming from our study are the rationale working hypothesis for such purposes.

Disclosure Statement

The authors have no Disclosure Statement.

References

- 1 Hansen TW, Thijs L, Li Y, Boggia J, Kikuya M, Björklund-Bodegård K, Richart T, Ohkubo T, Jeppesen J, Torp-Pedersen C, Dolan E, Kuznetsova T, Stolarz-Skrzypek K, Tikhonoff V, Malyutina S, Casiglia E, Nikitin Y, Lind L, Sandoya E, Kawecka-Jaszcz K, Imai Y, Wang J, Ibsen H, O'Brien E, Staessen JA: Prognostic value of reading-to-reading blood pressure variability over 24 hours in 8938 subjects from 11 populations. *Hypertension* 2010;55:1049-1057.
- 2 Mena L, Pintos S, Queipo NV, Aizpúrua JA, Maestre G, Sulbarán T: A reliable index for the prognostic significance of blood pressure variability. *J Hypertens* 2005;23:505-511.
- 3 Pessina AC, Palatini P, Sperti G, Cordone L, Libardoni M, Mos L, Mormino P, Di Marco A, Dal Palù C: Evaluation of hypertension and related target organ damage by average day-time blood pressure. *Clin Exp Hypertens* 1985;7:267-278.
- 4 Parati G, Ochoa JE, Bilo G: Blood pressure variability, cardiovascular risk, and risk for renal disease progression. *Curr Hypertens Rep* 2012;14:421-431.
- 5 Mancia G, Parati G, Pomidossi G, Casadei R, Di Rienzo M, Zanchetti A: Arterial baroreflexes and blood pressure and heart rate variabilities in humans. *Hypertension* 1986;8:147-153.
- 6 Palatini P, Rebollo G, Beilin LJ, Casiglia E, Eguchi K, Imai Y, Kario K, Ohkubo T, Pierdomenico SD, Schwartz JE, Wing L, Verdecchia P: Added predictive value of night-time blood pressure variability for cardiovascular events and mortality: the Ambulatory Blood Pressure-International Study. *Hypertension* 2014;64:487-493.
- 7 Manios E, Tsagalis G, Tsiygoulis G, Barlas G, Koroboki E, Michas F, Alexaki E, Vemmos K, Zakopoulos N: Time rate of blood pressure variation is associated with impaired renal function in hypertensive patients. *J Hypertens* 2009;27:2244-2248.
- 8 Zhang Y, Agnoletti D, Safar ME, Blacher J: Effect of antihypertensive agents on blood pressure variability: the Natrilix SR versus candesartan and amlodipine in the reduction of systolic blood pressure in hypertensive patients (X-CELLENT) study. *Hypertension* 2011;58:155-160.
- 9 Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, Poulter NR, Sever PS, ASCOT-BPLA and MRC Trial Investigators: Effects of beta blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. *Lancet Neurology* 2010;9:469-480.
- 10 Kimmel PL, Miller G, Mendelson WB: Sleep apnea syndrome in chronic renal disease. *Am J Med* 1989;86:308-314.
- 11 Winkelman JW, Chertow GM, Lazarus JM: Restless legs syndrome in end-stage renal disease. *Am J Kidney Dis* 1996;28:372-378.
- 12 Sabbatini M, Minale B, Crispo A, Pisani A, Ragosta A, Esposito R, Cesaro A, Cianciaruso B, Andreucci VE: Insomnia in maintenance haemodialysis patients. *Nephrol Dial Transplant* 2002;17:852-856.

- 13 La Manna G, Pizza F, Persici E, Baraldi O, Comai G, Cappuccilli ML, Centofanti F, Carretta E, Plazzi G, Coli L, Montagna P, Stefoni S: Restless legs syndrome enhances cardiovascular risk and mortality in patients with end-stage kidney disease undergoing long-term haemodialysis treatment. *Nephrol Dial Transplant* 2011;26:1976-1983.
- 14 Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D: A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;130:461-470.
- 15 Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves JW, Hill MN, Jones DH, Kurtz T, Sheps SG, Roccella EJ: Recommendations for blood pressure measurement in humans: an AHA scientific statement from the Council on High Blood Pressure Research Professional and Public Education Subcommittee. *J Clin Hypertens* 2005;7:102-109.
- 16 Parati G, Stergiou G, O'Brien E, Asmar R, Beilin L, Bilo G, Clement 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 practice guidelines for ambulatory blood pressure monitoring. *J Hypertens* 2014; 32:1359-1366.
- 17 Johns MW: A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14:540-545.
- 18 Walters AS, LeBrocq C, Dhar A, Hening W, Rosen R, Allen RP, Trenkwalder C: Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. *Sleep Med* 2003;4:121-132.
- 19 Weaver TE, Laizner AM, Evans LK, Maislin G, Chugh DK, Lyon K, Smith PL, Schwartz AR, Redline S, Pack AI, Dinges DF: An instrument to measure functional status outcomes for disorders of excessive sleepiness. *Sleep* 1997;20:835-843.
- 20 Weaver TE, Maislin G, Dinges DF, Bloxham T, George CF, Greenberg H, Kader G, Mahowald M, Younger J, Pack AI: Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. *Sleep* 2007;30:711-719.
- 21 Bastien CH, Vallières A, Morin CM: Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med* 2001 2:297-307.
- 22 Chung F, Subramanyam R, Liao P, Sasaki E, Shapiro C, Sun Y: High STOP-Bang score indicates a high probability of obstructive sleep apnoea. *Br J Anaesth* 2012;108:768-775.
- 23 Chung F, Yang Y, Liao P: Predictive performance of the STOP-Bang score for identifying obstructive sleep apnea in obese patients. *Obes Surg* 2013;23:2050-2057.
- 24 Kronborg J, Solbu M, Njølstad I, Toft I, Eriksen BO, Jenssen T: Predictors of change in estimated GFR: a population-based 7-year follow-up from the Tromsø study. *Nephrol Dial Transplant* 2008;23:2818-2826.
- 25 Tanner RM, Shimbo D, Dreisbach AW, Carson AP, Fox ER, Muntner P: Association between 24-hour blood pressure variability and chronic kidney disease: a cross-sectional analysis of African Americans participating in the Jackson heart study. *BMC Nephrol* 2015;16:84.
- 26 Pengo MF, Rossitto G, Bisogni V, Piazza D, Frigo AC, Seccia TM, Maiolino G, Rossi GP, Pessina AC, Calò LA: Systolic and diastolic short-term blood pressure variability and its determinants in patients with controlled and uncontrolled hypertension: a retrospective cohort study. *Blood Press* 2015;24:124-129.
- 27 Mallamaci F, Minutolo R, Leonardi D, D'Arrigo G, Tripepi G, Rapisarda F, Cicchetti T, Maimone I, Enia G, Postorino M, Santoro D, Fuiano G, De Nicola L, Conte G, Zoccali C: Long-term visit-to-visit office blood pressure variability increases the risk of adverse cardiovascular outcomes in patients with chronic kidney disease. *Kidney Int* 2013;84:381-389.
- 28 Chang TI, Tabada GH, Yang J, Tan TC, Go AS: Visit-to-visit variability of blood pressure and death, end-stage renal disease, and cardiovascular events in patients with chronic kidney disease. *J Hypertens* 2016;34:244-252.
- 29 Di Iorio B, Pota A, Sirico ML, Torraca S, Di Micco L, Rubino R, Guastaferro P, Bellasi A: Blood pressure variability and outcomes in chronic kidney disease. *Nephrol Dial Transplant* 2012;27:4404-4410.
- 30 Whittle J, Lynch AI, Tanner RM, Simpson LM, Davis BR, Rahman M, Whelton PK, Oparil S, Muntner P: Visit-to-Visit Variability of BP and CKD Outcomes: Results from the ALLHAT. *Clin J Am Soc Nephrol* 2016;11:471-480.

- 31 Parati G, Ochoa JE, Bilo G, Agarwal R, Covic A, Dekker FW, Fliser D, Heine GH, Jager KJ, Gargani L, Kanbay M, Mallamaci F, Massy Z, Ortiz A, Picano E, Rossignol P, Sarafidis P, Sicari R, Vanholder R, Wieczek A, London G, Zoccali C: Hypertension in Chronic Kidney Disease Part 2: Role of Ambulatory and Home Blood Pressure Monitoring for Assessing Alterations in Blood Pressure Variability and Blood Pressure Profiles. *Hypertension* 2016;67:1102-1110.
- 32 Hong K, Muntner P, Kronish I, Shilane D, Chang TI: Medication adherence and visit-to-visit variability of systolic blood pressure in African Americans with chronic kidney disease in the AASK trial. *J Hum Hypertens* 2016;30:73-78.
- 33 Torraca S, Palmese S, Sirico ML, Di Micco L, Salvi P, Di Iorio B: Does brachial blood pressure need to predict cardiovascular outcomes in end stage renal disease? An update. *Curr Hypertens Rev* 2013;9:60-65.
- 34 Walker S, Fine A, Kryger MH: Sleep complaints are common in a dialysis unit. *Am J Kidney Dis* 1995;26:751-756.
- 35 Neumann J, Ligtenberg G, Klein II, Koomans HA, Blankestijn PJ: Sympathetic hyperactivity in chronic kidney disease: pathogenesis, clinical relevance, and treatment. *Kidney Int* 2004;65:1568-1576.
- 36 Karasek M, Szuflet A, Chrzanowski W, Zylinska K, Swietoslowski J: Decreased melatonin nocturnal concentrations in hemodialyzed patients. *Neuro Endocr Lett* 2005;26:653-656.
- 37 Sim JJ, Rasgon SA, Derose SF: Review article: Managing sleep apnoea in kidney diseases. *Nephrology* 2010;15:146-152.
- 38 Martynowicz H, Porębska I, Poręba R, Mazur G, Brzecka A: Nocturnal Blood Pressure Variability in Patients with Obstructive Sleep Apnea Syndrome. *Advan ExpMed Biol* 2016;952:9-15.
- 39 Elias RM, Bradley TD, Kasai T, Motwani SS, Chan CT: Rostral overnight fluid shift in end-stage renal disease: relationship with obstructive sleep apnea. *Nephrol Dial Transplant* 2012;27:1569-1573.
- 40 Winkelman JW, Chertow GM, Lazarus JM: Restless legs syndrome in end-stage renal disease. *Am J Kidney Dis* 1996;28:372-378.
- 41 Drakatos P, Higgins S, Pengo MF, Kent BD, Muza R, Karkoulas K, Leschziner G, Williams A: Derived Arterial Stiffness is Increased in Patients with Obstructive Sleep Apnea and Periodic Limb Movements during Sleep. *J Clin Sleep Med* 2016;12:195-202.
- 42 Merlino G, Piani A, Dolso P, Adorati M, Cancelli I, Valente M, Gigli GL: Sleep disorders in patients with end-stage renal disease undergoing dialysis therapy. *Nephrol Dial Transplant* 2006;21:184-190.
- 43 Novak M, Shapiro CM, Mendelssohn D, Mucci I: Diagnosis and management of insomnia in dialysis patients. *Semin Dial* 2006;19:25-31.
- 44 Parker KP, Bliwise DL, Bailey JL, Rye DB: Daytime sleepiness in stable hemodialysis patients. *Am J Kidney Dis* 2003;41:394-402.
- 45 American Thoracic Society - Sleep Related Questionnaires [Internet] [cited 2017 Jun 19]. Available from: <http://www.thoracic.org/members/assemblies/assemblies/srn/questionnaires/>
- 46 Choi BCK, Pak AWP: A Catalog of Biases in Questionnaires. *Prev Chronic Dis* 2005;1:A13.