Comparative Prognostic Role of Nighttime Blood Pressure and Nondipping Profile on Renal Outcomes

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Key Words

Cardiovascular and renal outcomes • Nocturnal blood pressure • Dipping-nondipping status

Abstract

Different studies have addressed the predictive role of nighttime hemodynamics on cardiovascular and renal outcomes, although nocturnal blood pressure (BP) phenotypes (i.e. nondipping pattern and absolute nocturnal BP) have been found to be predictive of worse health outcomes. Furthermore, differences in both examined populations – ranging from healthy and younger subjects to those with overt cardiovascular disease – and study design (i.e. cross-sectional or longitudinal) make the interpretation of the suggested correlations difficult. Focusing on the kidney, we reviewed the literature addressing the impact of nocturnal BP phenotypes on renal outcomes in different populations by further dividing our search by study design. The evidence so far qualifies absolute nocturnal BP as a better predictor or determinant of kidney dysfunction as compared with the nondipping status. The magnitude of nocturnal hemodynamic load imposed at the glomerular level might be of higher prognostic value as compared with the integration of the pathophysiological mechanisms associated with impaired nocturnal BP variability. These findings underline the importance of noc-

turnal BP phenotypes, retrieved by ambulatory BP measurements, on age-dependent progressive kidney function decline and question whether, to what extent and in whom the reduced nocturnal BP or reverse nondipping BP profile to a normal pattern will be of benefit.

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Introduction

There is a two-way relationship between hypertension and kidney damage with adverse repercussions on both cardiovascular (CV) and kidney function [1]. The pathophysiological partnership between these two entities is getting established even in the preclinical stages and warrants proper evaluation and management of both increased blood pressure (BP) levels and progressive kidney impairment by means of microalbuminuria and decreased glomerular filtration rate (GFR). The magnitude of hemodynamic load is better reflected by ambulatory blood pressure monitoring (ABPM) compared to office BP evaluation [2]. Furthermore, ABPM measurements are more strongly associated with the development of microalbuminuria [3], the decline in GFR and the progression of proteinuria [4, 5] with respect to office BP.

Fig. 1. Methodological approach for defining the associations of nocturnal BP and circadian BP variability with renal outcomes. * Of the studies, 24 were both nocturnal BP and BP variability-oriented (sources: PubMed, Cochrane Database).

Although the definition of hypertension by using ABPM is based on the averaged 24 h systolic BP or diastolic BP >130 and >80 mm Hg respectively, there is increasing research to establish the relative importance of each of the components delivered by ABPM (i.e. daytime BP, nighttime BP, dipping status pattern) on hard and intermediate CV and renal outcomes. Although both the averaged absolute nighttime BP and the blunted nighttime BP decrease compared to daytime BP (i.e. nondipping status) invited heightened attention because of their association with adverse CV and renal outcomes [6, 7], their relative predictive value still remains controversial.

Therefore, in the present review we aimed to investigate whether either absolute nighttime BP or estimates of nighttime-focused circadian BP variability, namely dipping and nondipping patterns, are better associated with markers of kidney damage (i.e. microalbuminuria and GFR) and progression of nephropathy including the worst kidney-oriented clinical qualifications, namely end-stage kidney disease (ESRD) and hemodialysis.

In this perspective, we reviewed 73 clinical studies conducted between the beginning of 2000 and the end of October 2010, published in the English language, identified in PubMed and Cochrane Database by implementing the search terms: ‘nocturnal hypertension’, ‘nocturnal

BP’, ‘nighttime BP’, ‘dipping pattern’, ‘nondipping pattern’, ‘BP nondipping’, ‘BP dipping’ and each one of the aforementioned quoted phrases plus ‘microalbuminuria’, ‘kidney dysfunction’, ‘glomerular filtration rate’, ‘end-stage renal disease’ and ‘hemodialysis’. The resulting studies were divided per design; in these lines, 54 cross-sectional and 19 longitudinal studies were analyzed (fig. 1 – flowchart).

Searching in the Maze of Definitions

Dipping status is the at least 10% reduction in both systolic and diastolic BP during nighttime compared to daytime while BP fall less than 10% reflects the nondipping status. Dippers and nondippers exhibiting a BP fall more than 20% and increased averaged BP during nighttime versus daytime respectively compose two extreme subgroups, namely extreme dippers and reverse dippers [8]. Another way for defining dipping/nondipping status is night-to-day BP ratio and accordingly dippers lie between 0.90 and 0.80, nondippers between 0.91 and 1.00, extreme dippers below 0.80 and reverse dippers above 1.00. However, the lack of agreement in the above definitions and the selective implementation of nocturnal systolic or diastolic BP fall alone further complicate the clinical importance of the dipping/nondipping pattern.

According to the American Heart Association Council on High Blood Pressure Research and the European Society of Hypertension, nocturnal BP is considered within the normal range if the average of nighttime values is lower than 120/70 mm Hg [8, 9], whereas higher values than 125/75 mm Hg are deemed abnormal [8]. Nighttime is usually designated through arbitrarily defined fixed time intervals either wide (from 10 p.m. to 6 a.m.) or narrow (from midnight to 6 a.m.). The use of narrow fixed intervals in the absence of sleeping diaries is considered a more accurate estimate of sleeping BP [10]; consequently, not accounting for nighttime awakenings and daytime naps might contribute to misclassification of nocturnal hypertension.

In the majority of the studies so far, the proportion of successful readings during ABPM – as measure of testing accuracy – is not reported and additionally testing is usually performed only once. With respect to the latter, there is an ongoing debate for the reduced reproducibility of ABPM measurements potentially resulting in misclassification of dipping/nondipping status [11]. Furthermore, shift and nighttime work constitute a further issue not addressed by the design of the majority of ABPM-oriented studies and lastly, variations in nocturnal body position and diurnal physical activity may affect nighttime and daytime BP, respectively [12].

The nondipping profile is frequently accompanied by enhanced nocturnal BP, thus the discrimination between them might be an eternally uneven target to address. Furthermore, both nocturnal BP phenotypes are not always concomitantly present, hence the pathophysiological and clinical significance of each may differ. In a study of repeated ABPM, agreement in diagnosing nocturnal hypertension on the basis of two measurements was higher by using an absolute nocturnal systolic BP threshold rather than the percentage of nocturnal systolic BP fall [13]. Additionally, both the nondipping pattern and elevated nocturnal BP are associated with adverse cardiometabolic profile through pathophysiological mechanisms not yet fully elucidated. However, it could be reflected that sympathovagal imbalance [14], disturbed breathing during sleep [15], increased salt sensitivity [16], leptin and insulin resistance [17] and endothelial dysfunction [18], conjointly resemble a unified pathophysiological substrate promoting impaired nighttime hemodynamics.

Clinical and Pathophysiological Views of Altered Nighttime BP Patterns

The prevalence of the nondipping profile in essential hypertension is 20–30% and in those over 70 years esca-

lates into more than 40% [14, 19]. Among treated hypertensive patients, those with uncontrolled hypertension are more likely to be nondippers with respect to their well-controlled counterparts [20]. Interestingly, among those with refractory hypertension the prevalence of the nondipping pattern is triple or even quadruple as compared with the general hypertensive population and controlling for fluid volume expansion with incremental diuretic dosing may result in restoring of the dipping pattern [21]. The latter, in tandem with the observation that the nondipping pattern is more prevalent in older and blacks compared to younger and whites, respectively [22], highlights the importance of salt sensitivity as pathophysiological mediator of decreased circadian BP variability. The concept of abnormal sodium handling is further supported by the association of nondipping with chronic kidney disease and accelerated loss of kidney function [4, 23].

Several studies have shown an association between nighttime BP and measures of body size such as waist circumference and body mass index in both adults [24] and children [25]. Furthermore, overweight and obese hypertensive subjects as compared with their lean counterparts are more likely to be nondippers [26] and exhibit higher nighttime systolic BP values [27]. However, in a meta-analysis of several prospective population studies, different patterns of night-to-day systolic BP ratio demonstrated similar levels of body mass index [28]. Greater BP reductions were observed in obese compared to non-obese adolescents when shifting from high to low salt diet, suggesting an active involvement of insulin and leptin in the centrally sympathetic-mediated pressor effects [29].

Along the same lines, in a large cohort of 42,947 hypertensive patients [30] nondipping status was associated with both diabetes mellitus and obesity, while in 1,770 untreated nondiabetic hypertensive patients the nondipping profile was associated with metabolic syndrome after adjustment [31]. Lastly, in hypertensive patients without diabetes, insulin resistance has been associated with both the levels of nighttime BP [32] and the reduced nocturnal BP fall [33].

Increased sleeping time might protect from the nondipping pattern since day-night systolic BP change has been linearly associated with sleep duration [19], whereas poor sleep quality has been related to nocturnal hypertension [34]. Obstructive sleep apnea is closely associated with the nondipping profile and nocturnal hypertension beyond the estimates of body adiposity [15], and contributes to enhanced target organ damage including micro-

albuminuria [35–37] and CV morbidity [38]. In obstructive sleep apnea, increased sympathetic activity and decreased parasympathetic drive have been proposed as operating pathophysiological mechanisms associated with the nondipping pattern [38]. The interplay between sleep apnea and nighttime hemodynamics suggests that the ‘vulnerable airway’ may contribute at least partially to adverse CV and renal prognosis.

Among lifestyle attitudes, low physical activity showed a positive association with the nondipping profile; [39] by contrast, active smoking proved a yet not constant determinant for both nighttime BP [40, 41] and nondipping status [42, 43] extending the inconclusive association of smoking with hypertension in the nighttime. The surprising finding of the Dietary Approaches to Stop Hypertension (DASH) trial that reduced salt sensitivity was not accompanied by a dipping pattern could be explained by misclassification error to determine the dipping status [44].

Nocturnal BP Phenotypes and Renal Outcomes Longitudinal Studies

Decreased estimated GFR (eGFR) and increased urinary albumin excretion constitute independent predictors of adverse CV outcome [45]. Additionally, microalbuminuria candidates as a surrogate marker for kidney disease progression both in diabetic and nondiabetic patients with and without hypertension [46]. The differential impact of both the absolute nocturnal BP and nondipping profile taken alone on the renal outcomes has been investigated in several longitudinal studies (tables 1, 2).

Absolute nighttime BP demonstrated a constant association with ‘renal outcomes’ (i.e. the progression to ESRD requiring initiation of renal replacement therapy or the development of diabetic nephropathy as assessed by albuminuria) [6, 47]. Furthermore, a follow-up study of kidney biopsies in a small sample of normotensive patients with normoalbuminuric type 1 diabetes suggested that nighttime systolic and mean arterial BPs were the stronger predictive factors for the morphological glomerular changes of diabetic nephropathy [48].

On the other hand, there is a controversy regarding the prognostic role of the nondipping status on ‘renal outcomes’. Although a recent study in 112 type 2 diabetic patients showed that impaired nocturnal BP decline is an independent predictor of nephropathy progression [49], two other studies examining patients with and without chronic kidney disease revealed that after adjustment for common risk factors, the association of circadian BP variation with ESRD faded away [5, 50]. In addition, since

there are follow-up studies in diabetic subjects with or without hypertension that established associations of nondipping status with both glomerulopathy and increased urinary albumin excretion [47, 51], a post-hoc analysis that included patients with chronic kidney disease showed no correlation of nondipping status with the decline in renal function [52]. Taking this issue a step further, in elderly nonmacroalbuminuric diabetic patients the progression of albuminuria was associated solely with the phenotype of reverse nocturnal dipping and not with the nondipping pattern [53, 54]. Lastly, 177 kidney transplanted patients underwent ABPM after their grafts were independently functioning and were followed for at least 48 weeks after the intervention. Systolic diurnal BP variation was not associated with renal transplant function, and similarly the asleep-to-awake BP ratio did not correlate with the levels of the last available serum creatinine [55].

In addition to the aforementioned data, there are studies that examined at the same time the associations of nondipping status and nighttime BP with diverse renal outcomes. According to two studies enrolling normotensive and normoalbuminuric diabetic patients, both nondipping status and nighttime BP were significantly associated with the development of microalbuminuria [3] and the prospective change in urinary albumin excretion [56]. Moreover, a study that evaluated the antihypertensive effect of chronotherapy in 200 hypertensive patients showed that the reduction in urinary albumin excretion was correlated with both the decrease in nighttime BP and the increase in diurnal-to-nocturnal BP ratio [57]. In 217 patients with chronic kidney disease, night-to-day BP ratio and nighttime BP were predictive of ESRD, but the adjustment for 24 h systolic and daytime BP denied their prognostic impact [5].

Additional longitudinal studies aimed to address the differential impact of nondipping status over absolute nighttime BP on the same renal outcome. More specifically, in 1,040 elderly diabetic patients, baseline sleep pulse pressure and nighttime systolic BP were associated with the 2-year excreted albumin-to-creatinine ratio (ACR) levels as assessed by morning spot urine sample, whereas the baseline sleep-to-awake systolic BP ratio failed to predict the same outcome [58]. Along the same lines, in a cohort of 509 young diabetic subjects, baseline nighttime systolic BP was significantly related to excreted ACR during follow-up in contradistinction to nondipping status [59]. In Cox hazard regression analyses of the latter study, neither nocturnal BP fall nor nighttime BP had a significant contribution to the risk of developing

Table 1. Nocturnal BP and renal outcomes

Primary author	Study design	n	Type of cohort	Expression of nocturnal BP	Type of association	Outcome
Agarwal [5]	longitudinal	217	with CKD	nighttime BP	indifferent	ESRD
Redon [6]	longitudinal	79	nondiabetic with CKD stages 3 and 4	nighttime systolic BP	positive	ESRD
Felício [47]	longitudinal	70	diabetic with HTN	nighttime systolic BP	positive	diabetic nephropathy
Palmas [58]	longitudinal	1,040	diabetic	nighttime systolic BP	positive	2-year ACR
Marcovecchio [59]	longitudinal	509	diabetic (type 1)	nighttime systolic BP	positive	follow-up ACR
Hermida [57]	longitudinal	200	HTN	nighttime BP	positive	UAE
Lurbe [3]	longitudinal	75	diabetic adolescents and young adults with NTN	nighttime systolic BP	positive	microalbuminuria
Lengyel [56]	longitudinal	53	diabetic with NTN	nighttime diastolic BP	positive	change of UAE
Perrin [48]	longitudinal	19	diabetic adolescents with NTN	nighttime systolic BP	positive	diabetic glomerulopathy
Dost [62]	cross-sectional	2,105	diabetic children	nighttime diastolic BP	positive	microalbuminuria
Moran [67]	cross-sectional	1,180	older subjects with diabetes	nighttime BP	positive	ACR
Cuspidi [26]	cross-sectional	658	HTN	nighttime systolic/diastolic BP	indifferent	UAE
Pogue [66]	cross-sectional	617	HTN kidney disease	highest tertile of nighttime systolic BP	positive	increased proteinuria and lower eGFR
Syrseoudis [77]	cross-sectional	402	HTN	nighttime BP	positive	ACR
Cuspidi [11]	cross-sectional	375	HTN	nighttime BP	indifferent	UAE
García-Ortiz [64]	cross-sectional	353	HTN	nighttime systolic BP nighttime diastolic BP	positive positive	ACR lower GFR
Gaborieau [78]	cross-sectional	325	HTN	nighttime diastolic BP	positive	GFR
Leitão [63]	cross-sectional	270	diabetic	nighttime systolic/diastolic BP	positive	urinary ACR
Paoletti [79]	cross-sectional	244	with CKD	nighttime vs. daytime hypertension nighttime vs. daytime hypertension	positive positive	decreased creatinine clearance daily UAE
Agarwal [65]	cross-sectional	232	with CKD	nighttime BP	positive	worsening eGFR and increasing ACR
Rodrigues [80]	cross-sectional	188	diabetic	nighttime BP	indifferent	UAE rate
Lurbe [68]	cross-sectional	160	diabetics and nondiabetics	nighttime BP	positive	microalbuminuria and proteinuria
El-Gharbawy [81]	cross-sectional	145	HTN	nighttime BP	indifferent	UAE
Boulatov [60]	cross-sectional	140	GP	nighttime systolic BP	positive	ACR
Tsioufis [35]	cross-sectional	132	HTN	nighttime pulse pressure	positive	ACR
Duvnjak [61]	cross-sectional	116	normotensive type 1 diabetic	high nighttime diastolic BP	positive	high UAE
Paoletti [82]	cross-sectional	94	renal transplant recipients	nighttime diastolic BP	positive	serum creatinine
Knudsen [83]	cross-sectional	80	diabetic	night pulse pressure	positive	albuminuria
Soylu [72]	cross-sectional	79	NTN	nighttime systolic BP	indifferent	UAE
Bulatov [84]	cross-sectional	74	HTN	nighttime BP	positive	ACR
Tamura [85]	cross-sectional	68	HTN with renal failure	nighttime systolic BP	positive	urinary protein excretion
Stergiou [86]	cross-sectional	68	HTN	nighttime systolic BP	positive	UAE
Darcan [69]	cross-sectional	68	diabetic children and adolescents with NTN	nighttime BP	positive	microalbuminuria
Stergiou [87]	cross-sectional	50	diabetic adolescents and young adults	nighttime BP	positive	UAE
Tóth [88]	cross-sectional	46	diabetic	nighttime BP	positive	microalbuminuria
Andoh [89]	cross-sectional	45	nondiabetic with nephritic syndrome	nighttime BP	positive	proteinuria
Torbjörnsdotter [90]	cross-sectional	41	diabetic adolescents	nighttime MAP	positive	glomerulopathy changes
Torffvit [70]	cross-sectional	39	diabetic	nighttime systolic BP	positive	albuminuria and GFR
Cohen [71]	cross-sectional	37	diabetic	nighttime BP	positive	UAE
Mitsnefes [73]	cross-sectional	29	children with CKD	nighttime BP	indifferent	GFR

ACR = Albumin-to-creatinine ratio; CKD = chronic kidney disease; ESRD = end-stage renal disease; eGFR = estimated glomerular filtration rate; GP = general population; HTN = hypertension; NTN = normotension; UAE = urinary albumin excretion; MAP = mean arterial pressure.

Table 2. Circadian BP variability and renal outcomes

Primary author	Study design	n	Type of cohort	Expression of circadian BP variability	Type of association	Outcome
Agarwal [50]	longitudinal	322	with and without CKD	nondipping	indifferent	ESRD
Agarwal [5]	longitudinal	217	with CKD	nondipping	indifferent	ESRD
Knudsen [49]	longitudinal	112	diabetic	diastolic night-to-day BP ratio	positive	nephropathy progression
Redon [6]	longitudinal	79	nondiabetic with CKD stages 3 and 4	nondipping	indifferent	ESRD
Palmas [58]	longitudinal	1,040	diabetic	sleep-to-awake systolic BP ratio	indifferent	prediction of 2-year ACR
Palmas [53]	longitudinal	957	diabetic	nondipping reverse dipping	indifferent positive	progression of albuminuria progression of albuminuria
Marcovecchio [59]	longitudinal	509	diabetic	nondipping	indifferent	ACR
Palmas [54]	longitudinal	392	diabetic	nondipping reverse dipping	indifferent positive	worsening of albuminuria worsening of albuminuria
Davidson [4]	longitudinal	322	patients who were referred for ABPM	dippers nondippers	indifferent positive	progression GFR progression GFR
Hermida [57]	longitudinal	200	HTN	day-to-night BP ratio	positive	lower UAE
Haydar [55]	longitudinal	177	kidney transplant recipients	systolic BP diurnal variation	indifferent	prediction renal transplant function
Lurbe [3]	longitudinal	75	diabetic adolescents and young adults with NTN	nondipping	positive	microalbuminuria
Felício [47]	longitudinal	70	diabetic with HTN	nondipping	positive	final UAE
Lengyel [56]	longitudinal	53	diabetic with NTN	nondipping	positive	change of UAE
Torbjörnsdotter [51]	longitudinal	40	diabetic adolescents	nondipping	positive	glomerulopathy and hyper-filtration
Elung-Jensen [52]	longitudinal	34	with CKD	dipping	indifferent	decline in GFR
Shin [91]	longitudinal ¹	118	heart failure	nondipping	positive	lower eGFR
Astrup [92]	longitudinal ¹	104	diabetic	dipping	positive	GFR
Marinakis [93]	cross-sectional	2,800	HTN	nondipping	positive	ACR
Dost [62]	cross-sectional	2,105	diabetic children	diastolic nondipping	positive	microalbuminuria
Moran [67]	cross-sectional	1,180	older subjects with diabetes	dipping	indifferent	ACR
Wühl [94]	cross-sectional	1,152	with and without CKD	nondipping	indifferent	GFR
Björklund [95]	cross-sectional	1,057	elderly GP	nondipping	indifferent	urinary ACR
Muxfeldt [96]	cross-sectional	907	resistant HTN	nondipping	positive	nephropathy
Pogue [66]	cross-sectional	617	hypertensive kidney disease	nondipping nondipping	positive indifferent	microalbuminuria eGFR
Cuspidi [11]	cross-sectional	375	HTN	nondipping	indifferent	microalbuminuria
Cuspidi [97]	cross-sectional	355	HTN	nondipping	indifferent	microalbuminuria
García-Ortiz [64]	cross-sectional	353	HTN	nondipping	positive	ACR
Agarwal [23]	cross-sectional	336	with and without CKD	nondipping	positive	CKD and proteinuria
Leitão [63]	cross-sectional	270	diabetic	night-to-day BP ratios	indifferent	urinary ACR
Robles [98]	cross-sectional	256	with and without CKD	nondipping	positive	renal disease prevalence
Fava [99]	cross-sectional	249	NTN	systolic nondipping	positive	lower eGFR
Haydar [100]	cross-sectional	241	kidney transplant recipients	systolic BP diurnal variation	positive	lower GFR
Agarwal [65]	cross-sectional	232	CKD	night-to-day BP ratio	positive	ACR and lower eGFR
Lurbe [68]	cross-sectional	160	diabetics and non-diabetics	nondipping	positive	microalbuminuria and proteinuria
El-Gharbawy [81]	cross-sectional	145	HTN	day-minus-night BP	indifferent	microalbuminuria
Cuspidi [101]	cross-sectional	141	HTN	nondipping	indifferent	microalbuminuria
Wadei [102]	cross-sectional	119	kidney transplant recipients	nondipping	positive	lower GFR
Tsioufis [103]	cross-sectional	106	HTN	nondipping	positive	urinary ACR
Agarwal [104]	cross-sectional	103	CKD	nondipping nondipping	indifferent positive	eGFR albuminuria
Spallone [105]	cross-sectional	82	diabetic with NTN	nondipping	positive	UAE
Knudsen [83]	cross-sectional	80	diabetic	systolic night-to-day BP ratio	positive	albuminuria
Soylu [72]	cross-sectional	79	NTN	nondipping	positive	UAE
Hoshide [106]	cross-sectional	74	NTN	nondipping	indifferent	UAE
Bulatov [84]	cross-sectional	74	HTN	nondipping	positive	ACR

Table 2 (continued)

Primary author	Study design	n	Type of cohort	Expression of circadian BP variability	Type of association	Outcome
Darcan [69]	cross-sectional	68	diabetic children and adolescents with NTN	nondipping	indifferent	microalbuminuria
Torun [107]	cross-sectional	67	HTN	nondipping	positive	UAE
Fukuda [108]	cross-sectional	65	with CKD	nondipping	positive	lower creatinine clearance
Stella [109]	cross-sectional	61	diabetic	nondipping	positive	proteinuria
Andoh [89]	cross-sectional	45	nondiabetic with nephritic syndrome	night-to-day BP ratios	positive	proteinuria
Torffvit [70]	cross-sectional	39	diabetic	night-to-day ratio	indifferent	albuminuria and GFR
Pecis [110]	cross-sectional	39	diabetic with NTN	nondipping	positive	UAE
Cohen [71]	cross-sectional	37	diabetic	dipping	indifferent	UAE
Kooman [111]	cross-sectional	36	renal transplant patients with chronic transplant nephropathy	dipping of MAP	positive	creatinine clearance
Mitsniefes [73]	cross-sectional	29	children with CKD	nondipping	positive	lower GFR
Fukuda [112]	cross-sectional	26	with glomerulopathy	night-to-day ratio of MAP	positive	lower creatinine clearance
Yamamoto [113]	cross-sectional	25	HTN	night-to-day ratio of MAP	positive	lower eGFR

ABPM = Ambulatory blood pressure monitoring; ACR = albumin-to-creatinine ratio; CKD = chronic kidney disease; ESRD = end-stage renal disease; eGFR = estimated glomerular filtration rate; GP = general population; HTN = hypertension; MAP = mean arterial pressure; NTN = normotension; UAE = urinary albumin excretion.

¹ Cross-sectional analysis at baseline.

microalbuminuria [59]. In a further longitudinal study [4] with retrospective design enrolling 322 largely hypertensive patients, the nondipping status was associated with almost 16% decline in eGFR according to the Modification of Diet in Renal Disease formula; by contrast, eGFR remained unchanged among dippers after adjustment for confounders. Interestingly, in the same study the presence of daytime BP >139 mm Hg and 24 h systolic BP >136 mm Hg represented significant univariate determinants of eGFR decline, while nighttime systolic BP >127 mm Hg failed to predict the renal-guided outcome in the same setting, suggesting that the progression of chronic kidney disease could not be solely limited in the nocturnal hemodynamics [4]. However, the latter suggestion has been challenged by a recent study of 79 nondiabetic patients with chronic renal failure that investigated whether the nocturnal BP and nondipping pattern were prognosticators of ESRD development [6]. Accordingly, nighttime systolic BP >130 mm Hg was associated with doubling risk for ESRD and death, on top of other significant determinants, while neither daytime ambulatory BP nor nondipping status contributed to the examined renal outcome [6].

Cross-Sectional Studies

Cross-sectional studies (tables 1, 2) examining the relationship between circadian BP variation and kidney

function by means of eGFR and albuminuria resulted in conversing findings in different clinical settings, including newly diagnosed hypertension, treated hypertension, diabetes, and chronic kidney disease. However, the majority of the data so far suggest that microalbuminuria compared to eGFR is more constantly correlated with the nondipping profile. Furthermore, systolic and diastolic nocturnal BP levels were found associated with microalbuminuria [60–63], whereas some studies support a negative correlation with eGFR [64, 65]. In a cross-sectional analysis from the African American Study of Kidney Disease and Hypertension (AASK Cohort Study), recruiting African-Americans with hypertension and eGFR between 20 and 65 ml/min/1.73m² – without both diabetes and urinary albumin to creatinine excretion >2.5 mg/mg – it was shown that nondippers were more likely to demonstrate increased urinary albumin excretion in a 24-hour urine collection compared to dippers, while eGFR did not differ between the groups [66]. Additionally, participants in the highest tertile of nighttime systolic BP demonstrated higher prevalence of proteinuria and lower eGFR as compared with those residing in the middle and lower tertiles [66].

In a large study of 1,180 elderly patients with type 2 diabetes, absolute nighttime BP was correlated to ACR. By contrast, nocturnal dipping was associated with neither the ACR nor the categorically expressed albumin-

uria (i.e. normo-, micro-, and macro-). However, in multivariate regression analysis, when nighttime BP was added into the model along with office and awake BP, its significant association with ACR faded away [67]. In another study recruiting 270 type 2 diabetics, both the nighttime BP and night-to-day BP ratio were associated with urinary albumin excretion rate. Interestingly, after adjustment for confounders the association of nighttime BP with urinary albumin excretion rate remained significant, whereas the association of night-to-day ratio lost its significance. These findings suggest that crude increases in ambulatory nighttime BP compared to the nondipping phenomenon are more relevant in identifying diabetic patients at increased risk of microvascular complications [63]. Similar microalbuminuria-oriented findings were endorsed in adult [68] and pediatric [69] type 1 diabetic patients, further confirming the comparative predominance of absolute nighttime BP over circadian BP variability [70, 71]. By contrast, the superiority of nondipping status over nighttime BP on microalbuminuria can be supported only by two small studies – the first recruiting 79 normotensive subjects and the latter 29 children with chronic renal failure [72, 73].

Unloosing the Gordian Knot and Explaining the Controversy

By summarizing the above, there is mounting evidence of a positive association between markers of kidney damage and nocturnal hemodynamics including circadian BP variation. Although eGFR is not affected by measurement bias as compared with microalbuminuria, its association with nighttime BP phenotypes is not definitive so far. Moreover, first-void urine albumin excretion implemented in many studies [60, 62, 64] may better reflect crude nighttime hemodynamics, but its relationship with circadian BP variation is at least questionable.

With respect to the comparative importance of absolute nighttime BP values over nondipping status on the prognosis of renal outcomes, nighttime BP demonstrated a better association with both renal outcomes and markers of kidney dysfunction. The latter phenomenon could be explained by the fact that the absolute nocturnal BP expresses more accurately the real nocturnal hemodynamic load responsible in part for the hypertension-guided kidney damage and reflects better the basal BP (i.e. minimal BP needed for sufficient perfusion of the peripheral organs and tissues in resting conditions) [16]. From the pathophysiological standpoint, during the sleeping period the afferent arteriolar tone in the kidney is lower resulting in a more direct transmission of the systemic BP

to the glomerulus [6]. Therefore, high nocturnal BP values, above the aforementioned basal limits, increase the hemodynamic load imposed at the kidney level, triggering accelerated kidney damage [6].

On the other hand, the prognostic role of nondipping status on the renal outcomes could be explained by the fact that it is associated with sleep disruption, autonomic dysfunction and abnormal sodium handling [6, 15]. These associations reflect a dysfunction of fundamental regulatory BP mechanisms operating beyond the imposed hemodynamic load at the glomeruli level.

The divergent prognostic significance of the nocturnal BP and nondipping pattern could be also derived by the fact that nondipping is heavily dependent on daytime BP, and influenced by daytime confounders (i.e. physical and mental activity, seasonality, etc.) [74–76]. By contrast, nighttime BP is unsusceptible to the influence of daytime-oriented factors [75, 76]. Last but not least, it is known that the nondipping status is characterized by less reproducibility as compared with the absolute nighttime BP values [13]. However, increased nighttime BP and nondipping status usually coexist, and consequently their relative significance might be synergistic, additive or even indifferent in diverse clinical settings [6]. A recent study showed that dipping status and nocturnal hypertension could coincide in the same subjects and that absolute nighttime BP plays a significant role in the prediction of urinary albumin excretion over and beyond the nondipping status [77]. In the future, by including in the same prediction models, both determinants of nocturnal BP hemodynamics might help us to better crystallize their combined and separate impacts on the investigated renal outcomes.

Conclusions

The current evidence qualifies nocturnal BP as a stronger predictor or determinant of kidney damage compared to nondipping status, in different clinical settings including essential hypertension, type 2 diabetes mellitus and the elderly. The increased nocturnal hemodynamic load imposed at the glomerular microcirculation could partially explain the predictive superiority of absolute nocturnal BP over BP variability, however, the latter categorical parameter of ABPM could integrate important pathophysiological features related to the disrupted neurohormonal status of the investigated patients. In clinical practice, both nocturnal BP phenotypes may contribute to the antihypertensive management amelioration by intensifying the antihypertensive regimen, in-

roducing appropriate drugs with whole-day efficacy, and classifying the examined patients along with those with a heightened renal risk. Among hypertensive patients with impaired nocturnal hemodynamics, it is still unknown who benefits the most from nighttime BP reduction and whether normalizing increased nocturnal BP and/or reversing impaired BP variability contribute to better CV and renal outcomes.

Disclosure Statement

The authors have no conflicts of interest to declare.

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