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Circadian blood pressure profile in non-dialyzed patients with chronic kidney disease

ABSTRACT

Blood pressure follows a circadian rhythm; its physiological levels are higher during the day and lower at night. Ambulatory blood pressure monitoring (ABPM) facilitates the analysis of circadian blood pressure profiles and the diagnosis of nocturnal hypertension. Circadian blood pressure profiles are classified into 4 types: normal "dipper" profile with blood pressure falling by > 10% and ≤ 20%, "extreme dipper" profile with an excessive blood pressure fall (> 20%), "non-dipper" profile with reduced (≥ 10%) nocturnal blood pressure fall, and "reverse dipper" profile characterized by nocturnal blood pressure rise. Nocturnal hypertension is diagnosed for nocturnal systolic blood pressure of ≥ 120 mmHg or diastolic blood pressure of ≥ 70 mmHg. Abnormal circadian blood pressure profiles are observed in the majority of chronic kidney disease (CKD) patients not undergoing dialysis, as well as in the vast majority of kidney transplant recipients. Reduced nocturnal blood pressure fail, particularly in the "reverse dipper" profile, and nocturnal hypertension are associated with more severe hypertension-mediated organ damage, an increased cardiovascular risk, and faster progression of CKD. Hence, more extensive ABPM use is required in CKD to identify patients at high risk of complications. Further studies are also required to assess the influence of different therapeutic strategies on the circadian blood pressure profile in CKD patients.

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Key words: ambulatory blood pressure monitoring, circadian blood pressure profile, chronic kidney diseas

PHYSIOLOGICAL CIRCADIAN BLOOD PRESSURE PROFILES

Numerous physiological functions of the human body follow circadian rhythm profiles. Examples include the sleep/waking cycle, the circadian body temperature cycle, the circadian heart rate cycle, circadian hormone secretion cycles, circadian profiles of renal function — diuresis and sodium excretion, or circadian nervous system activity profiles [1, 2]. Blood pressure (BP) also follows a circadian rhythm profile; its physiological levels are higher during the day and lower at night. Circadian rhythms evolved as adaptational mechanisms to cyclic environmental changes, particularly to cyclic changes in sun exposure caused by the Earth's spinning around its axis [1].

The absence of a physiological decrease in blood pressure at night is associated with an increased risk of cardiovascular events [3–5] and chronic kidney disease [6, 7].

Ambulatory blood pressure monitoring (ABPM) facilitates the assessment of the circadian blood pressure profile in clinical practice. Specific indications for ABPM include the evaluation of nocturnal BP and nocturnal BP fail in patients with chronic kidney disease (CKD) and patients with vascularized organ transplantation [8–11].

This article aims to highlight the diagnostic and prognostic significance of ABPM measurements in non-dialyzed chronic kidney disease patients.

24-HOUR AMBULATORY BLOOD PRESSURE MONITORING

Hypertension is a key risk factor for cardiovascular disease, as well as a factor affecting the rate of CKD progression. The prevalence of arterial hypertension in non-dialyzed CKD patients is very high, reaching up to 86% [12]. In clinical practice, several methods are used to

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measure arterial blood pressure, including office blood pressure (oBP) measurement, standardized office blood pressure measurement, automated unattended office blood pressure measurement (without the presence of medical personnel), home blood pressure measurements (HBPM), and ABPM [13]. The methods differ in their availability, cost, repeatability, and prognostic value. The benefits of ABPM include the ability to evaluate circadian arterial blood pressure profiles and diagnose nocturnal arterial hypertension, white coat hypertension, and masked arterial hypertension [13]. Disadvantages of this method consist in its limited availability, high cost, and discomfort experienced by some patients in the course of examination [10, 11]. Another shortcoming of ABPM in relation to the assessment of circadian blood pressure profiles in CKD patients is unsatisfactory reproducibility or results [14].

Over the past decades, average ABPM values were documented to better identify the risk of cardiovascular events and present a stronger correlation with organ-related complications as compared to office blood pressure measurements [3, 5, 15–17]. In patients with CKD, ABPM is a better predictor of cardiovascular events and CKD progression as compared to office arterial blood pressure measurement [18].

When interpreting the results of ABPM, one must keep in mind the difference in the threshold values for the diagnosis of hypertension as compared to oBP measurements. For ABPM, the threshold values are ≥ 130/80 mmHg for the mean values of all-day systolic (SBP) and diastolic (DBP) arterial pressure, ≥ 135/85 mmHg for the mean values of SBP/DBP during the day (activity), and ≥ 120/70 mmHg for the mean values during the night (sleep) [10, 11].

CIRCADIAN BLOOD PRESSURE PROFILES

The simplest classification of circadian blood pressure profiles consists of 2 profiles, including the "dipper" profile with nocturnal blood pressure falling by more than 10%, and the "non-dipper" profile with the nocturnal blood pressure falling by no more than 10% or rising compared to daytime values [11]. Another method to describe these two arterial pressure profiles consists in calculating the night-to-day ratio, with values of < 0.9 corresponding to the dipper profile and values of ≥ 0,9 corresponding to the non-dipper profile [11, 13]. The 2018 ESH/ESC (European Society of Hypertension/European Society of Cardiology) guidelines do not specify whether the ratio should be calculated for SBP, DBP, or both SBP and DBP values [11]. It is, therefore, possible that one of the values falls by more than 10% while the other does not. In light of the above, most authors assume the change in SBP to be the determinant for profile classification [3, 5, 8, 19].

Another, more precise and more common classification, consists of 4 blood pressure profiles: normal nocturnal pressure fall ("dipper"), excessive nocturnal pressure fall ("extreme dipper"), no nocturnal pressure fall ("non-dipper", also known as "reduced dipper"), and an inverted blood pressure profile ("reverse dipper") [8, 9, 13, 16]. The criteria for recognizing these 4 blood pressure profiles are shown in Table 1.

CIRCADIAN BLOOD PRESSURE PROFILES IN CKD PATIENTS

Abnormal circadian blood pressure profiles in non-dialyzed patients with chronic kidney disease were demonstrated by Portaluppi et al. as early as the 1990s [20]. Studies analyzing the prevalence of different circadian blood pressure profiles in patients with CKD showed that the dipper profile is present in 22–35% of patients, the extreme dipper profile is present in 3–11% of patients, the non-dipper profile is present in 31–45% of patients, whereas the

Table 1. Classification of circadian blood pressure profiles

Profile name	Excessive nocturnal fall in blood pressure	Normal nocturnal fall in blood pressure	No nocturnal fall in blood pressure	Inversed nocturnal blood pressure profile
Common term	Extreme dipper	Dipper	Non-dipper' or reduced dipper	Reverse dipper
Change in arterial blood pressure	Fall by > 20%	Fall by > 10% and ≤ 20%	fall by ≥ 10%	No fall or rise
Night-to-day ratio	Night/day BP < 0.8	Night/day BP ≥ 0.8 and < 0.9	Night/day BP ≥ 0.9 and < 1.0	Night/day BP > 1.0

reverse dipper profile is present in 17–35% of patients [21–23]. According to a somewhat simplified interpretation, only 3 out of every 10 non-dialyzed CKD patients present with a normal blood pressure profile while other 4 patients present with the non-dipper profile, 2 patients present with nocturnal blood pressure higher than during the day (reverse dipper), and 1 patient presents with excessive nocturnal fall in blood pressure (extreme dipper). It should also be added that the incidence of abnormal arterial pressure profiles increases with the CKD stage [24, 25].

In addition to CKD, conditions associated with the absence of nocturnal fall in blood pressure include obstructive sleep apnea, obesity, diabetic neuropathy, autonomic dysfunction, orthostatic hypotension, high sodium intake in sodium-sensitive patients, elderly age, and sleep disturbances in shift workers [11].

CIRCADIAN BLOOD PRESSURE PROFILES AND SUBCLINICAL ORGAN DAMAGE

Hypertension is a risk factor for cardiovascular events and cardiovascular death. Before clinically overt cardiovascular disease develops in patients with hypertension, subclinical hypertension-mediated organ damage (HMOD) can be detected in the heart, kidney, vessels, or brain; the presence of HMOD facilitates identification of patients with an increased risk of clinically overt cardiovascular disease and cardiovascular death. Examples of HMOD include left ventricular hypertrophy (LVH) and increased aortic pulse wave velocity (PWV) indicative of excessive arterial stiffness. Adverse prognostic value of LVH and elevated PWV has been documented in patients with CKD [26, 27].

The relationship between circadian arterial pressure profiles and HMOD has been the subject of a number of studies in patients with arterial hypertension. Patients with the non-dipper profile presented with more advanced HMOD features, namely greater left ventricular hypertrophy, impaired left ventricular systolic and diastolic functions, and increased arterial stiffness [27]. Several studies analyzing this issue in patients with CKD were also published. The absence of nocturnal blood pressure drop has been shown to be related to left ventricular hypertrophy and left ventricular systolic dysfunction [23, 25, 29, 30]. Importantly, the absence of nocturnal blood pressure drop has been reported to be related to the progression of LVH over a one-year follow-up period [29].

A strong correlation between nocturnal systolic blood pressure and left ventricular hypertrophy was demonstrated in CKD patients [23]. A negative correlation was observed between the nocturnal blood pressure drop and the LV mass index [30]. In another study, the degree of left ventricular hypertrophy was the largest in patients with the reverse dipper profile [23]. However, no link was demonstrated between the absence of a nocturnal blood pressure drop and the carotid artery intima-media thickness (IMT) [23, 30].

NOCTURNAL HYPERTENSION

The phenomenon of nocturnal hypertension (NH) is also worth mentioning when discussing the issue of abnormal blood pressure profiles. ABPM is the only non-invasive method facilitating the diagnosis of this condition. The diagnostic criterion of NH consists in the average nocturnal SBP of ≥ 120 mmHg or the average nocturnal DBP of ≥ 70 mmHg [9, 11, 13]. The incidence of nocturnal hypertension in CKD patients is 57–60% [23, 31]. Nocturnal hypertension is associated with more pronounced HMODs: left ventricular hypertrophy, IMT thickening, and increased arterial stiffness [23, 31]. CKD and NH patients also present with lower glomerular filtration rate (GFR) values compared to CKD patients without nocturnal hypertension [31].

Hypertension is a risk factor for subclinical brain damage such as cerebral microhemorrhage, silent brain strokes, or periventricular hyperintensities. In CKD patients, the incidence of these subclinical brain injury indicators is increasing with the stage of chronic kidney disease [32, 33]. Unfortunately, no circadian blood pressure profiles or the prevalence of NH were analyzed in the studies documenting this relationship. Potential relationships between the absence of nocturnal pressure drop/NH and the subclinical brain injury indicators in CKD patients remain open for research.

ABNORMAL CIRCADIAN BLOOD PRESSURE PROFILES AND CKD ONSET/PROGRESSION

The absence of nocturnal arterial pressure drop in patients with CKD is associated with faster CKD progression and a higher risk of end-stage kidney disease [22, 31, 34]. In a large population of patients with CKD

and arterial hypertension, abnormal circadian blood pressure profiles were associated with a decreased GFR and larger proteinuria [21]. A similar adverse effect was shown for the nocturnal blood pressure load defined as the percentage of the nocturnal blood pressure measurements of ≥ 120 mmHg for SBP or ≥ 70 mmHg for DBP [35]. Increased nocturnal blood pressure load was associated with an increased risk of achieving the renal endpoint of doubling the baseline creatinine level or dialysis therapy being required [35].

In patients with hypertension, the non-dipper profile and LVH are predictors of *de novo* development of CKD [6]. Moreover, even in patients with controlled hypertension, the reduced GFR of < 60 mL/min/1.73 m^2 and albuminuria were demonstrated to be more common in patients with the non-dipper and reverse dipper profiles than in patients with the dipper profile [7].

THE PROGNOSTIC VALUE OF ABNORMAL CIRCADIAN BLOOD PRESSURE PROFILES

Analyzes involving large populations of patients with arterial hypertension revealed a negative impact of the non-dipper and reverse dipper profiles as compared to the dipper profile [3, 5]. A recent study [16] has also shown that the impact of the extreme dipper profile is more adverse compared to the regular dipper profile.

Evidence for the adverse impact of the absence of nocturnal blood pressure drop was also collected in the CKD patient population [22, 36], with the cardiovascular prognosis being the worst and the risk of achieving the renal endpoint being the highest in patients with the inverted circadian blood pressure (reverse dipper) profile [22].

The increased nocturnal blood pressure load was also associated with increased overall and cardiovascular mortality, an increased risk of cardiovascular events and reaching the renal endpoint [35].

These are further arguments for ABPM being routinely used in CKD patients to identify patients at an increased risk of cardiovascular events and CKD progression.

CIRCADIAN BLOOD PRESSURE PROFILES IN KIDNEY TRANSPLANT RECIPIENTS

In kidney transplant recipients, ABPM has an advantage, compared to oBP, regarding the ability to predict HMOD and cardiovascular events [37, 38]. Circadian blood pressure profiles were also studied in patients after kidney transplantation. In one of the studies, the normal dipper profile was observed in only 17% of transplant recipients, with the remaining 52% and 31% of recipients presenting with the non-dipper and the reverse dipper profiles, respectively [37]. In another study carried out on 260 recipients with a mean eGFR of 58 mL/min/1.73 m^2, the night-to-day SBP ratio of ≥ 1, corresponding to the inverted blood pressure profile (reverse dipper), was observed in 33% of patients, and 74% of patients presented with nocturnal hypertension [39]. Comparing the oBP and ABPM measurement results, the authors of the study concluded that relying on oBP leads to incorrect therapeutic decisions being made at 37% of office visits [39].

A systematic literature review including 22 studies and 2078 subjects revealed that non-dipper or reverse dipper profiles blood pressure profiles identified kidney transplant recipients at a higher risk of transplant loss and with more pronounced cardiovascular abnormalities [38].

A reverse dipper profile observed in an ABPM measurement after a kidney transplant was a strong predictor of a cardiovascular event or graft failure in further follow-up [37].

CHRONOTHERAPY OF HYPERTENSION IN CHRONIC KIDNEY DISEASE

For many years, significant interest has been observed regarding possible modification of the timing of the administration of antihypertensive drugs to CKD patients. An uncontrolled study carried out in a small group of CKD patients revealed that administration of one of the antihypertensive drugs in the evening, instead of the morning, restored the nocturnal pressure drop in 88% of patients [40]. Another study carried out in a much larger group of CKD patients demonstrated the beneficial impact of one or more hypotensive drugs administered in the evening on the circadian blood pressure profile and the reduction in the rate of cardiovascular events [41].

A meta-analysis of data from 3732 patients with CKD and arterial hypertension revealed that when the antihypertensive drugs are administered in the evening, the incidence of the non-dipper profile is reduced by 40%; this, however, did not translate to the overall or cardiovascular mortality rates [42].

However, a study comparing 2 antihypertensive treatment strategies in which 1) all drugs were administered in the morning or 2) all drugs were administered in the evening, or 3) an additional drug was administered in the evening in addition to drugs administered in the morning, observed no difference with regard to the extent of nocturnal hypertension in a group of African American CKD patients [43]. These ambiguous observations require verification in well-designed studies in larger patient populations.

Among therapeutic interventions with potential beneficial effects on the daily blood pressure profiles in CKD, administration of sodium-glucose co-transporter-2 (SGLT2) has also been mentioned. The authors of the concept used the results of experimental studies and case reports as the rationale [44]. Also worth mentioning are the results of the randomized SACRA study, even though it had not been carried out on CKD patients. The study revealed a reduction in the nocturnal blood pressure in patients with type 2 diabetes and uncontrolled nocturnal hypertension following the inclusion of SGLT2 empagliflozin [45]. Considering that the inclusion of empagliflozin in the treatment of patients with type 2 diabetes, concomitant cardiovascular disease, and chronic kidney disease has reduced the risk of cardiovascular death and hospitalization [46], this direction of search for novel modalities improving the circadian blood pressure profile in CKD patients seems to be particularly interesting.

SUMMARY

Abnormal circadian blood pressure profiles are observed in most non-dialyzed CKD patients. ABPM facilitates the evaluation of the circadian blood pressure profile and diagnosis of nocturnal hypertension. Four circadian blood pressure profiles have been identified based on nocturnal changes in blood pressure, including the normal dipper profile, the abnormal extreme dipper (excessive blood pressure drop), non-dipper (insufficient blood pressure drop), and reverse dipper (nocturnal rise in blood pressure) profiles. Nocturnal hypertension is defined as SBP/DBP ≥ 120/70 mmHg. Reduced nocturnal blood pressure dips, particularly the reverse dipper profile, and nocturnal hypertension are associated with an increased cardiovascular risk and faster progression of CKD. Research on therapeutic interventions which would positively impact the daily arterial pressure profile in CKD patients is ongoing.

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