Central blood pressure and nighttime blood pressure in patients with non-diabetic chronic kidney disease

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Abstract

Introduction. Arterial hypertension is a well-known risk factor of both cardiovascular complications and faster progression of chronic kidney disease (CKD). There is growing evidence that central blood pressure (BP) and nighttime BP may have an advantage in predicting the risk of cardiovascular complications and the progression of CKD in comparison with the traditional office BP measurements. The aim of this study was to evaluate the central BP and nighttime BP in non-diabetic CKD patients with no, or only mild proteinuria i.e. autosomal dominant polycystic kidney disease (ADPKD) or IgA nephropathy (IgAN).

Material and methods. Forty patients with CKD stage 3 or 4 were enrolled into the study. In each patient the measurement of peripheral and central BP was conducted, as well as the assessment of pulse wave velocity (PWV) and the 24-hour blood pressure monitoring (ABPM).

Results. Despite the lower office and central BP values in patients with IgAN in comparison to patients with ADPKD, both studied groups did not differ in the mean BP in the 24-hour ABPM. In the entire studied group a significant positive correlation was found between the augmentation pressure and age, as well as between the augmentation index - AIx% and age. Moreover, a significant positive correlation between the decrease of nighttime BP and eGFR was observed. Additionally, a significant positive correlation between PWV and age was found.

Conclusions.

1. Patients with ADPKD and IgAN, despite the differences in office and central BP do not differ in respect of the mean BP in the 24-hour ABPM.
2. In both groups of patients vascular stiffness increases with age and deteriorating kidney function.
3. Lower decrease of nighttime blood pressure is related to the worse kidney function in patients with non-diabetic CKD.

key words: central blood pressure, nighttime blood pressure decrease, chronic kidney disease

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Background

Arterial hypertension is one of the most aggravating factors in the development and progression of chronic kidney disease (CKD) regardless of its etiology. The blood pressure assessment done traditionally on the brachial artery and has been used for over a 100 years for the diagnosis of arterial hypertension and monitoring the effects of antihypertensive therapy.

The elevated values of blood pressure measured on the brachial artery (peripheral blood pressure) are associated with the increased risk of the development of cardiovascular diseases, incidence of stroke and development and progression of CKD [1], while the decrease of the peripheral blood pressure leads to the lower incidence of aforementioned morbidities [2].

The results of CAFÉ [3] study seem to suggest that the values of blood pressure measured on the brachial artery (peripheral blood pressure) not always correspond to the values of blood pressure in the aorta (central blood pressure). However, there is continuously more and more evidence, suggesting that the central blood pressure — which is the true perfusion pressure of the central nervous system, heart and kidneys — may differ from the peripheral blood pressure because of the effect of blood pressure amplification. This effect is caused by the gradual decrease of the arterial wall elasticity with the decrease of the diameter of the arteries. This effect may result in the increased central blood pressure [4]. The pulse wave generated by the contraction of the left ventricle spreads in the arterial branches and tends to reflect in the sites of arterial diameter reduction (mostly when the muscular type arteries turns into the arterioles) and then proceeds upwards "back" to the aorta. As a consequence of this phenomenon the shape of pulse wave in the aorta can be regarded as a sum of overlapping "primary" pulse wave generated by the left ventricle and the "secondary" reflected wave returning to the aorta from distal parts of the vasculature [5].

The central blood pressure increases with the higher arterial stiffness which, in turn can be influenced predominantly by the arterial hypertension, hyperlipidemia and tobacco use [6, 7]. Moreover the central blood pressure rises with age what can be explained by the more pronounced increase of stiffness of the central than peripheral arteries [5, 8].

The results of various clinical and experimental studies led to the conclusion that increased arterial stiffness is an independent predictor of the risk of all-cause mortality [9], cardiovascular mortality [10], as well as ischemic heart disease and stroke [11].

As it was already mentioned arterial stiffness tends to increase with age, and is sometimes regarded as one of the markers of senility. Nevertheless, arterial stiffness is also increased in young patients with CKD [12, 13]. Moreover, the results of some studies shown that arterial stiffness increases across the stages of CKD [13–15].

As it was mentioned before the central blood pressure and the pulse wave velocity (PWV) — a surrogate of the arterial stiffness are linked to the cardiovascular risk in the general population as well as in patients with hypertension and CKD. However, there have been no studies conducted that would assess the detailed profile of central blood pressure in non-diabetic CKD patients with mild- or no-proteinuria.

The results of some small clinical studies revealed that in patients with CKD nondipping circadian blood pressure pattern is common [16]. This is probably caused by both hypervolemia and increased arterial stiffness. Moreover, the non-dipping blood pressure profile and increased central blood pressure have been described in patients with diabetes and diabetic nephropathy i.e. chronic morbidities usually characterized by significant proteinuria [17]. It has been also postulated that the achievement of normal nocturnal blood pressure (e.g. by administering additional antihypertensive drugs during the bed time at night) could be the most important target of treatment in this group of patients [18].

In patients with CKD of non-diabetic etiology the less pronounced dipping, or even reversed dipping (paradoxical increase of blood pressure during night-time) has also been described [19, 20]. However, the exact pathomechanism of the abovementioned phenomenon has not been described so far. Also, if the nondipping/reversed dipping phenomenon can lead to faster progression of CKD has not been unequivocally confirmed. There is however some data available, that in fact nondipping can accelerate CKD progression [21].

Additionally, it is worth to mention that in patients with essential hypertension the nighttime blood pressure seems to be the strongest predictor of the occurrence of cardiovascular events. Still, achieving the target nighttime blood pressure remains one of the most difficult obstacles to surpass in the treatment of arterial hypertension [22].

It seems then, that the elevated nighttime blood pressure in CKD patients with the acceptable blood pressure control during the day may have a great impact on the target organ damage in the course of arterial hypertension. However, there have been no studies conducted so far, that would precisely assess

the profiles of nighttime blood pressure in CKD patients with no- or only mild proteinuria.

The aim of this study was to assess the central blood pressure and nighttime blood pressure in non-diabetic CKD patients with no- or only mild proteinuria i.e. autosomal dominant polycystic kidney disease (ADPKD) and IgA nephropathy (IgAN).

Material and methods

Forty adult patients with CKD stage 3 or 4 (eGFR 15.0–59.9 ml/min/1.73 m^2) have been enrolled into the study. The eGFR was calculated according to the MDRD formula. The patients' mean age was 49.0 ± ± 14.7 years. The etiology of non-diabetic CKD was confirmed during the careful clinical evaluation as follows: ADPKD in 30 patients and IgAN based on kidney biopsy in 10 patients.

Patients with severe heart or liver failure with expected survival time shorter than 12 months were excluded from the study. Moreover, patients with significant heart arrhythmias, including atrial fibrillation also could not be enrolled, as those types of arrhythmias preclude the accurate pulse wave analysis. The study protocol was adherent to the Declaration of Helsinki and all patients had given the written informed consent for the participation in the study.

In all of the patients a standard blood pressure measurement on the left brachial artery after 10 minute rest has been conducted. Patients had their backs supported and the brachial artery was at the level of the heart. Next the noninvasive central blood pressure and PWV measurements have been done using the applanation tonometry using the SphygmoCor Device (AtCor Medical Pty Ltd, West Ryde NSW, Australia). Central blood pressure measurements have been done after a 10 minute rest in a supine position. The tonometer was placed on the left radial artery in the site that the pulse was best palpable.

Then, the PWV assessment in aorta has been conducted. The tonometer was placed on the common carotid (CCA) and femoral arteries, respectively in the sites where the pulse was best palpable. In this method the time variable of the PWV is calculated relatively to the tip of the "R" wave in the ECG that is conducted simultaneously. Thus, when the heart rate differed more than 5 beats per minute between the measurements on the CCA and femoral artery, the result was discarded and the measurement repeated.

Next, the 24-hour ABPM has been conducted in all of the enrolled patients using the A&D TM-2430 device (A&D Instruments LTD, Abingdon, UK). The measurements have been taken every 15 minutes during daytime and nighttime. Blood pressure values gathered between 6 AM and 10 PM were regarded as daytime values and from 10 PM to 6 AM as nighttime values. Morning blood pressure surge (MBPS) was calculated as a difference between mean blood pressure from the 2 hours after awakening and the mean from 3 measurements obtained during nighttime (the lowest recorded measurement and the measurements obtained 15 minutes before and after the lowest one).

The statistical calculations have been done with the Statistica 10.0 software (StatSoft Poland, Cracow, Poland). Shapiro-Wilk test was used to test the variables distribution, Kruksal-Wallis test was used to assess the differences between variables. Correlation coefficients were calculated using Spearman's rank correlation. Results are shown as means with 95% confidence index (CI) or as median values with interquartile range (IQR) when appropriate. Differences were considered significant when $p < 0.05$.

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Results

Patients with ADPKD and IgAN were in a similar age (Table I). Mean serum creatinine concentration in the whole group of patients was 166 (123–209) µmol/L and the eGFR was 47.3 (39.9–54.8) ml/ /min/1.73 m^2. There were no significant differences in the eGFR in the patients with ADPKD and IgAN (Table I). The mean body mass index (BMI) in the whole group of patients was 25.7 (24.4–26.9) kg/ /m^2. There was no significant difference in the BMI between both studied groups of patients (Table I). There was also no significant difference in the number of antihypertensive medications taken by the patients enrolled to both studied groups (Table I).

The mean values of peripheral blood pressure in the whole group of patients were: systolic blood pressure (SBP) — 136 (130–142) mmHg; diastolic blood pressure (DBP) — 83 (80–87) mmHg. Patients with ADPKD had higher peripheral DBP in comparison with patients with IgAN. Moreover, a trend ($p = = 0.07$) towards higher peripheral SBP pressure in patients with ADPKD has been found. No differences in pulse pressure (PP) have been found between the studied groups (Table II).

The mean values of central blood pressure in the whole group of non-diabetic CKD patients were as follows: SBP: 128 (122–134) mmHg, DBP: 84 (81– –88) mmHg, pulse pressure: 44 (39–48) mmHg,

Table I. Clinical characteristics of patients with ADPKD or IgA nephropathy

	ADPKD n = 30	IgAN n = 10	p
Age (years)	50.6 (44.7–56.4)	47.8 (36.2–59.8)	0.15
BMI [kg/m^2]	26.0 (24.6–27.4)	24.6 (21.7–27.4)	0.77
Serum creatinine concentration [μmol/l]	175 (118–233)	132 (100–164)	0.65
eGFR [ml/min/1.73 m^2]	43.6 (34.9–52.2)	50.1 (45.0–56.2)	0.49
Number of antihypertensive drugs	2.36 ± 1.37	2.33 ± 1.33	0.97

ADPKD — autosomal polycystic kidney disease; IgAN — IgA nephropathy; BMI — body mass index; eGFR — estimated glomerular filtration rate

Table II. The comparison of the peripheral and central blood pressure as well as the pulse wave velocity in patients with ADPKD or IgA nephropathy

	ADPKD n = 30	IgAN n = 10	p
SBP brachial artery [mmHg]	139 (132–146)	125 (107–142)	0.07
DBP brachial artery [mmHg]	85 (81–89)	75 (68–82)	0.02
PP brachial artery [mmHg]	54 (48–60)	50 (35–65)	0.41
SBP central [mmHg]	130 (124–137)	115 (97–132)	0.03
DBP central [mmHg]	86 (82–90)	76 (68–83)	0.01
PP central [mmHg]	44 (39–50)	39 (26–53)	0.30
AP [mmHg]	15.1 (11.5–18.6)	12.0 (4.5–19.5)	0.38
AIx% [%]	32.1 (26.1–38.2)	27.6 (18.5–36.6)	0.24
PWV [m/s]	9.05 (7.86–10.23)	6.68 (2.51–10.90)	0.1

ADPKD — autosomal polycystic kidney disease; IgAN — IgA nephropathy; SBP — systolic blood pressure; DBP — diastolic blood pressure; PP — pulse pressure; AP — augmentation pressure; AI% — augmentation index; PWV — pulse wave velocity

Table III. The comparison of the 24-hour blood pressure monitoring in patients with ADPKD or IgA nephropathy

	ADPKD n = 30	IgAN n = 10	p
SBP daytime [mmHg]	140 (134–146)	141 (126–155)	0.86
DBP daytime [mmHg]	89 (86–92)	83 (72–94)	0.1
SBP nighttime [mmHg]	119 (111–128)	125 (111–139)	0.34
DBP nighttime [mmHg]	72 (68–76)	70 (60–80)	0.5
Nighttime SBP decrease [mmHg]	16 (13–19)	11 (6–16)	0.11
Nighttime DBP decrease [mmHg]	19 (16–22)	16 (9–23)	0.43
MBPS [mmHg]	29.3 (20.1–37.8)	19.5 (from –18.1 to –57)	0.4
Heart rate [beats/minute]	71 (67–75)	68 (63–72)	0.053

ADPKD — autosomal polycystic kidney disease; IgAN — IgA nephropathy; SBP — systolic blood pressure; DBP — diastolic blood pressure; MBPS — morning blood pressure surge

augmentation pressure (AP) 15.0 (11.9–18.1) mmHg, augmentation index (AIx%) 31.3 (26.4–36.2) %.

Patients with ADPKD were characterized by higher values of central SBP and DBP (Table II). No differences in the PP, nor the central blood pressure parameters (AP, AIx%) have been found between the two groups (Table II).

In the 24-hour ABPM analysis the mean SBP in the whole group was: 139 (134–145) mmHg, while DBP was: 88 (85–91) mmHg. During nighttime the values were: 120 (112–126) mmHg and 73 (69–77), respectively.

The mean dipping values in the whole studied group were: SBP 14.5 (11.4–17.6) mmHg, and DBP 17 (13.8–20.2) mmHg. The dipping exceeding 10% occurred in 52% of patients regarding SBP and 72% of patients regarding DBP. The mean morning blood pressure surge — MBPS was 22 (21–36) mmHg.

There was a trend (p = 0.053) towards a lower heart rate in the patients with IgAN comparing to the patients with ADPKD. There were no other significant differences regarding ABPM values in both studied groups (Table III).

Correlation analysis

A significant positive correlations between the parameters of central blood pressure: AP; AIx% and

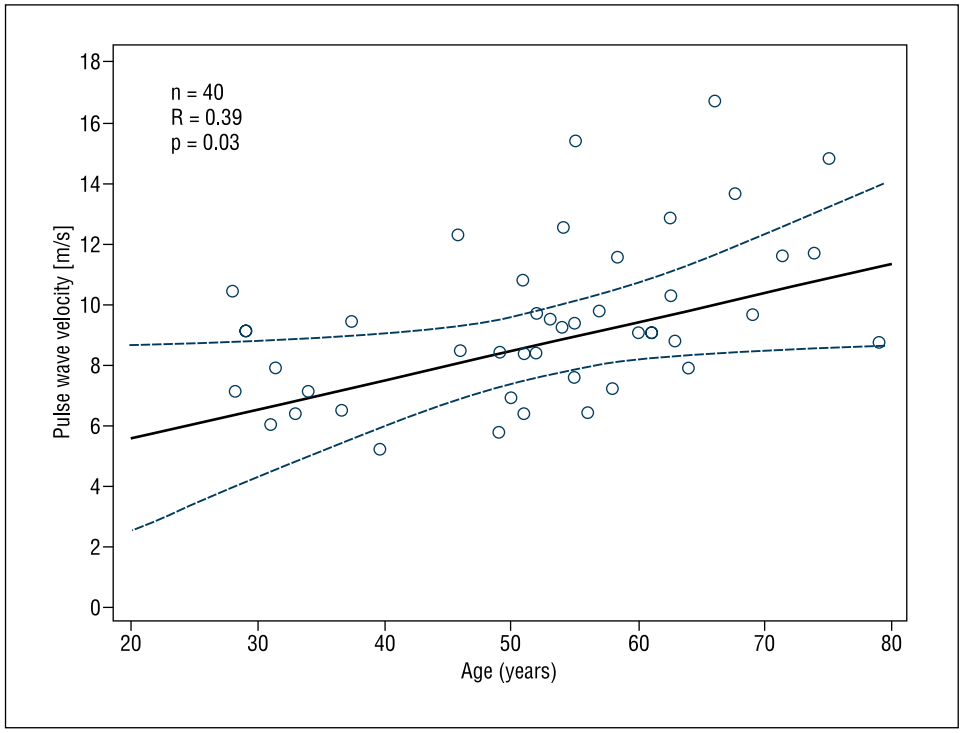

Figure 1. The correlation between the pulse wave velocity and the patients' age

age were found — R = 0.47; p = 0.004 i R = 0.52; p = 0.002, respectively.

In the whole studied group a significant positive correlation (R = 0.39; p = 0.03) between the PWV and age was found (Fig. 1). Additionally, a significant negative correlation (R = –0.42; p = 0.03) between the diastolic nighttime blood pressure decrease and PWV was observed.

Moreover, there has been a significant positive correlation found between the decrease of nighttime blood pressure and eGFR. The correlation coefficients for SBP and DBP were: R = 0.49; p = 0.018 and R = 0.42; p = 0.04, respectively (Fig. 2A, B).

Discussion

The aim of the present study was to assess the central blood pressure and nighttime blood pressure in non-diabetic stage 3 and 4 CKD patients. Only patients with CKD caused by ADPKD or IgAN and no- or low proteinuria were enrolled into this study.

There were no significant differences in the age, excretory kidney function, nor the BMI between both studied groups of patients (ADPKD and IgAN respectively, Table I).

Patients with IgAN were characterized by lower office peripheral blood pressure than patients with ADPKD (Table II). Interestingly, these differences have not been confirmed in the 24-hour ABPM. It would be interesting to assume that this difference could be due to the described increased sympathetic nervous activity in ADPKD patients [23]. This could result in a more pronounced "white coat" effect in patients with ADPKD, but so far it is only a vague hypothesis, which needs confirmation in a larger group of patients. Nevertheless, there was a trend (p = 0.053) towards a slower mean heart rate in patients IgAN in comparison with patients with ADPKD, what might be regarded as a rough surrogate of the sympathetic nervous activity. The fact that the patients did not differ in the number of prescribed antihypertensive drugs (Table I) also seems to somehow strengthen this hypothesis.

Regarding the central blood pressure parameters, similarly to the peripheral blood pressure, patients with IgAN had lower values of central SBP and DBP. It should be noted, however, that there were no significant changes in the central blood pressure parameters — AP and AIx% were similar in both groups (Table II).

As it was mentioned above, there were no significant differences between the values of blood pressure during daytime and nighttime in the 24-hour blood pressure monitoring, despite the differences in office blood pressure values. This has again confirmed the low accuracy of office blood pressure measurements in patients with CKD.

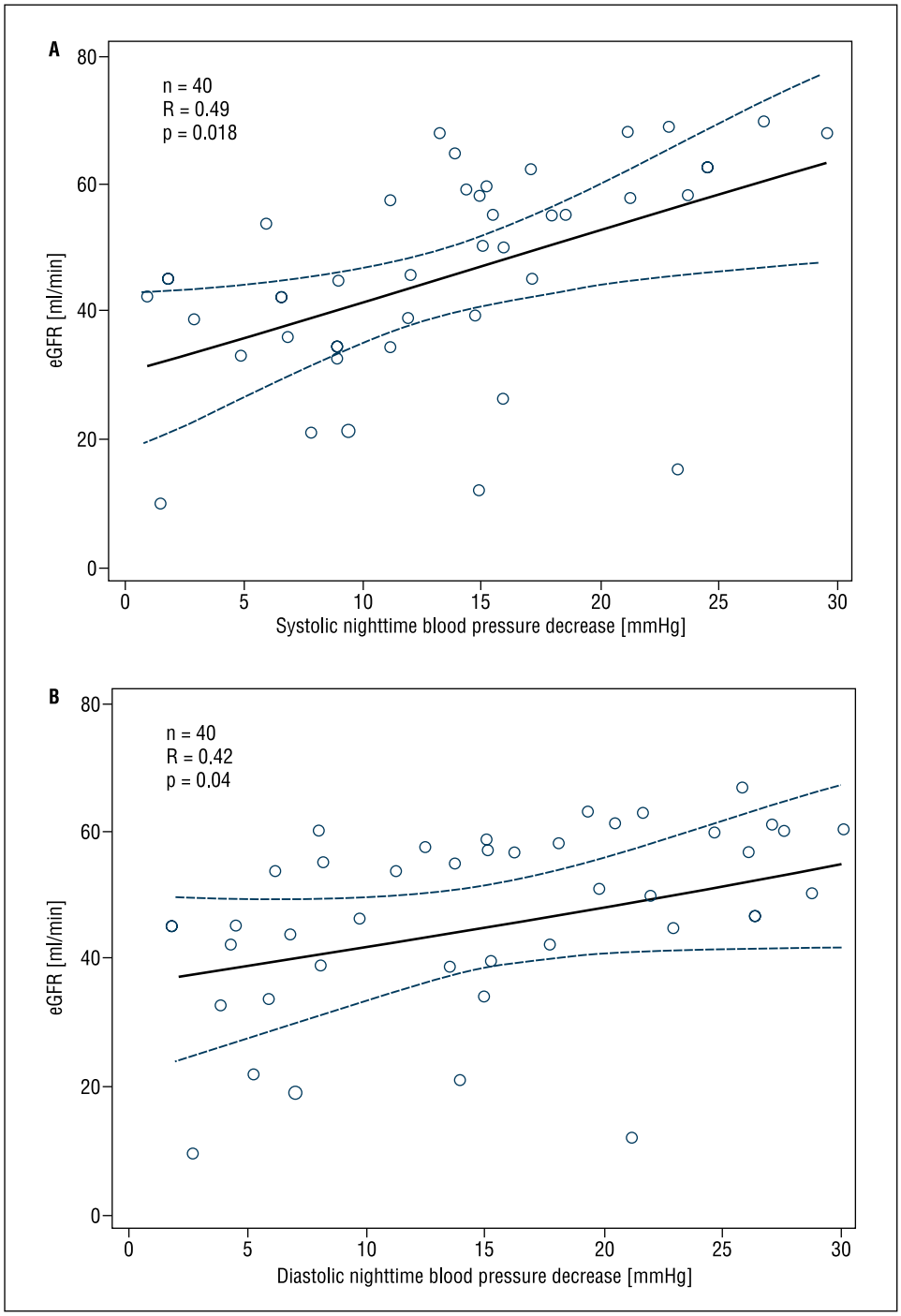

Figure 2. The correlation between the eGFR and the decrease of systolic nighttime blood pressure (**A**) and diastolic nighttime blood pressure (**B**)

Interestingly, the majority of our patients had lower mean blood pressure values during the night (dipping) what stays in contrast to some studies conducted before [17, 24]. This might, however, be a surrogate of careful antihypertensive treatment in patients under a nephrological supervision, as it was shown that the appropriate dosing of antihypertensive medication may change the dipping patterns and reduce the cardiovascular risk [25].

In the correlation analyses a significant positive correlation was found between the parameters of central blood pressure and the patients' age. This is in agreement with some other clinical studies conducted so far in patients with essential hypertension as well as in general population [5, 6].

Interestingly, a significant correlation between the nighttime blood pressure decrease and the deterioration of kidney function (positive correlation with

eGFR, negative with serum creatinine concentration — Fig. 2) was found. These results are also in concordance with the clinical studies conducted previously [19, 20]. It needs to be underlined that the nondipping blood pressure pattern is a strong independent risk factor of both cardiovascular and general mortality [26].

What is more, a significant positive correlation between the PWV and the patients' age was found (Fig. 1). This seems to suggest the increase of arterial stiffness with age in patients with CKD stage 3 or 4. In this manner, this population of patients resembles the general population and patients with terminal renal failure [27].

Moreover, a significant negative correlation between the diastolic dipping blood pressure pattern and PWV was found. This would seem to suggest that the lesser diastolic dipping is related to the more pronounced stiffness of aorta. This is important in the context of the fact that both PWV and the nighttime blood pressure are recognized non-classical risk factors of cardiovascular complications in this group of patients.

In conclusion the results of our study suggest that patients with ADPKD and IgAN, despite the differences in office and central BP, do not differ in respect of the mean values of BP in the 24-hour ABPM. Additionally, in both groups of patients vascular stiffness increases with age and deteriorating kidney function. Finally, lower decrease of nighttime blood pressure is related to the worse kidney function in patients with non-diabetic CKD.

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