Original Paper

Different Relevance of Peripheral, Central or Nighttime Blood Pressure Measurements in the Prediction of Chronic Kidney Disease Progression in Patients with Mild or No-Proteinuria

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Key Words

Central blood pressure • Ambulatory blood pressure monitoring • Chronic kidney disease

Abstract

Background/Aims: Arterial hypertension is one of the leading factors aggravating the course of chronic kidney disease (CKD). It seems that the novel parameters used in the assessment of the blood pressure (BP) load (i.e. central blood pressure, nighttime blood pressure) may be more precise in predicting the cardiovascular risk and the progression of CKD in comparison with the traditional peripheral blood pressure measurements in the office conditions. The aim of the study was to assess the impact of the central, or nighttime blood pressure on the progression of CKD in patients with mild or no-proteinuria (autosomal, dominant polycystic kidney disease or IgA nephropathy). **Methods:** In each of the enrolled 46 patients with CKD stage 3 or 4, serum creatinine concentration was assessed, eGFR (MDRD) was calculated, also central blood pressure and pulse wave velocity (PWV) was assessed and the 24-hour ambulatory blood pressure monitoring (ABPM) was conducted at the beginning of the study and then repeated after one-year observation period. **Results:** During the observation period mean eGFR decreased from 44.1 (33.2-50.6) mL/min to 36.7 (29.7-46.3) mL/min. No significant differences were observed in the peripheral blood pressure or central blood pressure parameters. After one-year observation period the values of diastolic blood pressure dipping

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during the night significantly decreased from 16 (13-19) mmHg to 12 (10-15) mmHg; $p < 0.05$. The values of systolic dipping during the night or the mean BP values recorded in ABPM did not change significantly. Additionally, no significant differences in the PWV values were found. In the multivariate regression model the change of serum creatinine concentration was explained by the initial diastolic dipping values. **Conclusion:** 1. In patients with CKD stages 3 or 4 and mild or no- proteinuria, peripheral and central blood pressure did not change significantly during a one-year observation period despite the significant decline of eGFR and seems not to participate in the CKD progression. 2. Reduced magnitude of the diastolic dipping, which reflects the increase of diastolic blood pressure load during the nighttime, may play an important role in the pathogenesis of deterioration of kidney function in these patients.

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Introduction

Chronic kidney disease (CKD) is one of the most important risk factors of the increased morbidity, mortality and worsening of the quality of life. The risk of the aforementioned complications strongly increases across the stages of CKD.

One of the most aggravating factors influencing the progression of CKD (regardless of its aetiology) is arterial hypertension. The traditional technique of blood pressure measurement on the brachial artery is now roughly 110 years old and still is the most common examination used for the diagnosis and monitoring of arterial hypertension. Increased blood pressure is directly related to the more pronounced risk of cardio-vascular morbidities, stroke and CKD progression [1]. Moreover, almost any decrease in peripheral blood pressure leads to the diminished risk of aforementioned complications [2].

It is important to stress, that in fact it is the central blood pressure (i.e. the blood pressure in the ascending aorta) that creates the real perfusion pressure of the most vital organs – the central nervous system, heart and the kidneys. It has been well documented, that the central blood pressure (CBP) not always fully corresponds with the peripheral blood pressure measured on the brachial artery [2-4]. This is due to the amplification of the blood pressure caused by the reduction of the vessel wall elasticity with the diminishing of the lumen diameter [5] and the existence of so called reflected pulse waves. Briefly: the pulse wave generated by each left ventricle contraction spreads down the arterial tree and then reflects in the points the lumen diameter abruptly decreases or the artery branches. Such reflected wave travels backwards thus overlapping the primary pulse wave. In consequence the shape of pulse wave in aorta is a sum of the primary and reflected waves [6].

As it was already mentioned, arterial stiffness also influences the central blood pressure. Results of various clinical trials led to the conclusion that the increased vascular stiffness is the risk factor of increased cardiovascular and general mortality, ischemic heart disease and stroke [7-9]. Vascular stiffness is increased even in young subjects with CKD [10, 11] and tends to increase across the stages of CKD [12, 13].

Despite the fact that central blood pressure (CBP) and the pulse wave velocity (PWV – an excellent arterial stiffness surrogate) [14, 15] are linked to the increased cardiovascular risk there have been few studies conducted regarding the influence of CBP and PWV on the progression of CKD in hypertensive patients especially with non-proteinuric kidney diseases, or with only mild proteinuria.

The results of clinical studies with low number of enrolled patients conducted until now, revealed that in patients with CKD the dipping blood pressure pattern during the night is usually absent [16]. This was robustly described mainly in CKD patients with diabetic nephropathy i.e. with a morbidity usually characterized by severe proteinuria [17, 18]. Still, even in patients with non-diabetic CKD the loss of blood pressure dipping, or even a paradoxical nighttime blood pressure increase has been observed in some studies [19, 20].

There is some data suggesting that the lack of dipping of blood pressure during the night can exaggerate the progression of CKD in this group of patients [21, 22], nonetheless this phenomenon has been so far only cursorily elucidated in CKD patients with mild or no-proteinuria.

The aim of the current study was then the assessment of the influence of the central blood pressure parameters, as well as, the nighttime blood pressure dipping on the progression of CKD in patients with only small extent of proteinuria i.e. the autosomal dominant polycystic kidney disease (ADPKD) or IgA-nephropathy.

Materials and Methods

Forty-six adult CKD patients, from three different Departments of Nephrology in the mean age of 49 (45-54) years were enrolled into this prospective study. The inclusion criteria were the occurrence of either autosomal dominant polycystic kidney disease (ADPKD) – 34 patients or IgA nephropathy. The diagnosis of IgA-nephropathy was always confirmed by the histopathological examination of the kidney biopsies – 12 patients. Only patients in CKD stage 3 or 4 – i.e. with estimated glomerular filtration (eGFR) between 15 and 59.9 mL/min/1.73m² were enrolled into the study. The eGFR was calculated according to the MDRD formula [23].

The exclusion criteria were: severe cardiac and/or liver insufficiency with the life expectancy below 12 months and severe heart arrhythmias (including atrial fibrillation) that precluded the accurate pulse wave recording and analyses. Also, patients with previously diagnosed obstructive sleep apnea were not enrolled into the study. Moreover, to maximize the studied group homogeneity, patients with proteinuria exceeding 1g/24- hours were not enrolled.

All patients received antihypertensive treatment based on the renin-angiotensin system (RAS) blockers, e.g. angiotensin converting enzyme inhibitor (ACEi) or blockers of type 1 angiotensin II receptor (ARBs). In 19 cases these agents were used in monotherapy (11 and 8 patients for ACEi or ARBs, respectively), 14 patients were treated with a combination of RAS blockers and calcium channel blocker, 5 with RAS blockers and diuretic, 4 with the combination of all of the 3 aforementioned medications and 3 with RAS blockade, calcium channel inhibitor and beta-blocker. Only patients with no change in the pattern of antihypertensive therapy during the last 2 months were enrolled into the study.

In case of the resistant form of arterial blood pressure occurrence (lack of the “office” blood pressure control despite the above mentioned multi drug therapy with more than 3 antihypertensive drugs and obligatory diuretic as one of these compounds), patients were ruled-out from the study.

In all patients a peripheral blood pressure on the brachial artery was assessed using the typical procedure (Korotkov modification of Riva-Rocci method in the seated position after at least 10-minute rest with the back and arm fully supported). Additionally, a non-invasive measurements of the central blood pressure and PWV assessment were conducted with the SphygmoCor device (AtCor Medical Pty Ltd., West Ryde NSW, Australia).

The central blood pressure assessment was conducted after an at least ten-minute rest in the supine position. The blood pressure was measured 3 times in the supine position on the hand on which the previously described BP assessment was returned higher values, then the averaged BP was used as a reference value for the CBP measurement. The tonometer was placed over the radial artery in the point, where the pulse was best palpable. Only the measurements with the Operator Index exceeding 85% were considered satisfactory, else the measurement was repeated.

The next step was the assessment of the carotid-femoral PWV (cfPWV) during the same visit. The examination was also done in the supine position. The tonometer was placed over the left common carotid artery and left femoral artery in the places the pulse was best palpable. The distance between the carotid and femoral arteries has been calculated accordingly to the manufacturer’s suggestions as a difference in the distance from the suprasternal notch and the femoral artery minus the distance between the suprasternal notch and the carotid artery. In the used method of PWV assessment the time of pulse progression is measured relatively to the peak of the “R” wave in the simultaneously conducted ECG recording. Thus, if

the heart rate varied over 5 beats per minute between the recordings, the examination was repeated. The average of 2 consecutive PWV measurements was the value used in the statistical analyses.

All of the CBP and PWV measurements at the beginning of the study and after one year have been conducted always by only one experienced physician.

Finally, also during the same visit, a 24-hour blood pressure monitoring was started using the A&D TM-2430 devices (A&D Instruments LTD, Abbingdon, UK). The BP measurements were recorded every 15 minutes during the whole 24-hour observation period. Blood pressure values obtained between 6 AM and 10 PM were regarded as daytime and from 10 PM to 6 AM as night-time. Morning blood pressure surge (MBPS) was calculated as a difference between mean blood pressure from the two hours after awakening and the mean from 3 measurements obtained during night-time (the lowest recorded measurement and the measurements gathered 15 minutes before and after the lowest one).

The statistical analyses were done with the Statistica 10.0 software (StatSoft Poland, Cracow, Poland). Shapiro-Wilk test was used to test the variables distribution; Wilcoxon signed rank test was used to assess the differences between variables. Correlation coefficients were calculated using Spearman's rank correlation. Multiple regression models were built for variables that reached $p < 0.2$ significance in the correlation analyses. 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 $p < 0.05$.

Results

Thirty-seven out of the 46 enrolled patients have completed the study. Among the 9 excluded subjects 1 required renal replacement therapy before the end of observation period, 3 had their antihypertensive treatment modified due to the lack of adequate hypertension control and 5 patients withdrew their consent for the study.

During the one-year observation period there was a significant ($p < 0.001$) increase in the serum creatinine concentration from 166 (132-201) $\mu\text{mol/l}$ at the beginning of the study to 182 (114-250) $\mu\text{mol/l}$ after 1 year; thus the eGFR decreased from 44.1 (33.2-50.6) mL/min/1.73m^2 to 36.7 (29.7-46.3) mL/min/1.73m^2 , respectively (Fig.1).

No significant differences were found in the peripheral blood pressure between the beginning of the study and the control visit (Table 1). Also, the central blood pressure did not change during the observation period. Moreover, the central blood pressure parameters ($\text{AIx\%}$, $\text{AIx\%@75 BPM}$, AP) remained stable (Table 1).

There were no significant differences in the mean daytime and nighttime values of blood pressure recorded in the ABPM (Table 2). A significant decrease occurred in the magnitude of diastolic dipping – from 16 (10-13) mmHg to 12 (10-15) mmHg; $p < 0.05$, while the magnitude of the systolic dipping remained unchanged – 14 (12-17) mmHg and 12 (10-14) mmHg, respectively. Also the magnitude of the morning blood

Fig. 1. The change of the eGFR during the 1-year observation period in all individual patients (also the mean values are provided). eGFR = estimated glomerular filtration rate.

pressure surge (MBPS) was stable – 28 (20-36) and 28 (20-37) mmHg, respectively. The prevalence of non-dippers was not significantly different ($p=0.45$) between the beginning of the study – 10 (27%) patients, and after 1-year observation period – 13 (35%) patients respectively.

Moreover, no significant differences were found regarding the PWV at the beginning of the study and after 1-year observation period – the values were: 8.93 (7.86-10.00) m/s and 9.33 (8.49-10.16) m/s; $p=0.69$, respectively.

In the correlation analyses there was no impact of the peripheral nor central blood pressure values observed on the change of serum creatinine concentration. However, a significant negative correlation was found between the change of creatininemia and the magnitude of diastolic dipping during the night ($R=-0.59$; $p=0.002$) at the beginning of the study.

No significant correlations were found between the PWV values and serum creatinine concentration, nor the change of creatininemia during the observation period.

To test, whether this was not only an incidental finding we have built a multiple regression model with the change of serum creatinine concentration as a dependent variable. These analyses revealed a somewhat weaker, but still significant dependence of the change of serum creatinine concentration on the magnitude of the initial diastolic dipping $R^2=0.21$; $p=0.04$. The other variables chosen (systolic central blood pressure, mean systolic daytime BP recorded in ABPM) did not retain in the regression model.

Discussion

In the current prospective clinical study, despite the fact of significant kidney function worsening during a one-year observation period we have found no significant differences in the values of blood pressure measured over the brachial artery, nor any differences in the central blood pressure values nor the augmentation pressure or augmentation index.

In the light of our findings it seems that there is no strong rationale for the assessment of CBP in CKD patients, what is in general concordance with the results of most recent studies [24]. However, it has been recently shown, that in advancing CKD the tonometry-based method of measurement of CBP may underestimate the CBP values, mostly because

Table 1. Comparison of the values of peripheral (brachial) BP and central BP during the observation period. BP = blood pressure, SBP = systolic blood pressure, DBP = diastolic blood pressure, PP = pulse pressure

Variable	At the beginning of the study	After 1 year	p
Brachial SBP [mmHg]	138 (131-143)	136 (131-142)	0.90
Brachial DBP [mmHg]	84 (80-87)	86 (81-92)	0.16
Brachial PP [mmHg]	54 (48-59)	52 (48-55)	0.55
Central SBP [mmHg]	129 (123-135)	127 (122-133)	0.87
Central DBP [mmHg]	85 (81-88)	86 (82-89)	0.15
Central PP [mmHg]	44 (39-49)	42 (38-45)	0.54
Augmentation Pressure [mmHg]	15 (12-18)	13 (11-16)	0.43
Augmentation Index – Alx% [mmHg]	32 (27-37)	30 (25-36)	0.79
Augmentation Index – Alx% @75 BPM [mmHg]	26 (21-30)	24 (19-30)	0.84

Table 2. Comparison of blood pressure values recorded during the 24-hour ambulatory blood pressure measurement. SBP = systolic blood pressure, DBP = diastolic blood pressure, MBPS = morning blood pressure surge

Variable	At the beginning of the study	After 1 year	p
Day-time mean SBP [mmHg]	139 (134-145)	136 (129-142)	0.93
Day-time mean DBP [mmHg]	87 (84-90)	88 (80-96)	0.98
Night-time mean SBP [mmHg]	121 (114-126)	120 (113-127)	0.23
Night-time mean DBP [mmHg]	72 (68-76)	77 (70-83)	0.10
Systolic dipping [mmHg]	14 (12-17)	12 (10-14)	0.21
Diastolic dipping [mmHg]	16 (13-19)	12 (10-15)	<0.05
MBPS [mmHg]	28 (20-36)	28 (20-37)	0.74

the increased arterial stiffness [25, 26]. In our patients there was a significant increase of serum creatinine concentration found during the observation period, so it is possible that the advancing renal insufficiency might confound the accuracy of the measurement. On the other hand, there was no significant increase of arterial stiffness surrogate (carotid-femoral PWV), this only underlines the necessity of further studies regarding this topic.

Indeed, in a recent study in which the central blood pressure in patients with CKD stage 3 and albuminuria were compared with matched patients with no CKD, there were no significant differences found regarding the central blood pressure parameters between these two groups of patients [27], suggesting that the impact of kidney function on central BP may only be present in more advanced CKD [28]. This also raises a question concerning the importance of targeting these parameters in early stages of CKD. Of note, the central BP parameters assessed in such a large cohort of CKD patients were similar to the obtained in our study [27].

We have found a significant difference in the magnitude of diastolic dipping during the night between the beginning of the study and after a 1-year observation period (Table 2). However, the prevalence of patients presenting the dipping BP pattern did not change significantly – 27 vs 24 of 37 patients; $p=0.45$. The prevalence of dippers in our study was quite high for patients with CKD. In a study by Choi et al. [29] the loss of dipping was reported in 56% of patients with coronary artery calcifications and in 44% of patients without coronary artery calcifications. In our populations the non-dipping pattern occurred in 27% of patients at the beginning of the study and 35% after the one-year observation period. This difference may arise from the fact that none of our patients had diabetes and diabetic patients were quite common in a cited study – 46.3%, and diabetes is known to cause disturbances in the autonomic nervous system. Nonetheless, the lack of dipping was a risk factor for coronary artery calcifications in the study by Choi et al. what seems to be in general concordance with our study where we have found that the difference in dipping is related to kidney function loss in patients with mild or no proteinuria [29]. The loss of dipping of the diastolic blood pressure seems to be a crucial factor which leads to the increase load of diastolic blood pressure during the night-time in these patients [20].

Similarly, it was shown by Liu et al. that in chronic haemodialysis patients the loss of dipping during the night is associated with a high incidence of cardiovascular complications, profound autonomic nervous system dysfunction and poor long-term survival [30].

In our study the linear relation between the inadequate dipping of the blood pressure during the night and kidney function deterioration was further confirmed using a multiple regression analysis which suggests, that indeed the lower degree of the diastolic blood pressure dipping during the night, the faster kidney damage occurs. This is in agreement in a recent study from Chinese population in which a similar cohort of patients – suffering from IgA nephropathy – was examined [31]. In these study patients with IgA-nephropathy and non-dipping blood pressure pattern were characterized by higher serum concentrations of cystatin-C and lower eGFR, along with more severe renal tissue damage in the histopathological examination than in patients with preserved dipping blood pressure pattern.

Moreover, in a recently published study from Korea, Cha et al. observed that adequate BP control and the “dipper” blood pressure pattern were associated with subtler eGFR and proteinuria changes in a prospective, one-year observation of almost 400 CKD patients [32], what also confirms our findings.

Maintained circadian rhythm of BP variability is a consequence of among others: autonomic (sympathetic) nervous system function and sleep-activity cycle. The fact, that patients with preserved dipping have slower CKD progression may be linked to the better preserved autonomic nervous system function that is damaged (increased sympathetic activity [33]) in the course of CKD. Also, circadian rhythms of renin, angiotensin II and aldosterone (RAA system) have been described. The release of the aforementioned hormones as a result of increased sympathetic activity has been well documented so one may hypothesize that preserved dipping is a reflection of lesser extent of RAA system activation

regardless of the fact that the anti-hypertensive treatment in our patients was based on RAA system blockade.

Also, sleep deprivation is common in CKD. This can be reflected in the absence of dipping and a tendency towards faster CKD progression [34].

Still, the most obvious explanation would be the fact that the blood pressure load (defined as the proportion of elevated - above the normal range - blood pressure measurements) is higher in non-dipping patients with more advanced CKD. These patients are more susceptible for damage caused by hypertension because of the failure of intrarenal blood flow autoregulation due to activation of the tubulo-glomerular feedback which leads to opening the pre-glomerular capillaries and easier transmission of the systemic hypertension directly to the glomeruli. It was shown that increased intra-glomerular pressure is one of the leading factors in the pathogenesis of faster progression of CKD [35, 36].

Our study has some limitations. The most important one is relatively small study group with quite high percentage of patients lost to follow up. This circumstance arises from, among others, the fact that we have strictly abided all enrolment criteria in order to maximize the homogeneity of the studied group. Taking this fact into consideration we have decided to calculate the results of patients with ADPKD and IgA-nephropathy as a one group. The main factor which justified this maneuver was the fact that these patients were characterized by a low or absence of proteinuria and relatively low rate of progression of CKD. Still, even in such a modest study group we have identified an important factor leading to accelerated kidney function loss.

It has to be underlined that the results of all measurements involving applanation tonometry that were used in our study are characterized with high inter-operator variability. To avoid this obvious fault all of the measurements have been conducted by a single operator (P.K.) in all 3 distant centres (Katowice, Warsaw, Wrocław). We feel that the single-operator based study guaranteed the accuracy and repeatability of measurements, thus allowing us to draw conclusions from the study, even if the studied population was not high. Other drawback might be the rather short observation period, this was caused by the fact that a lot of patients were lost to follow up, mostly because the withdrawal of consent for the study continuation and by the high transplant rate.

Conclusion

1. In patients with CKD and stages 3 or 4 with mild or no- proteinuria the central blood pressure did not change during a one-year observation period in spite of significant decline of eGFR and seems not to participate in the CKD progression. 2. The reduced magnitude of the diastolic blood pressure dipping, which reflects the increase of diastolic blood pressure load during the night-time, may play an important role in the pathogenesis of deterioration of kidney function in these patients.

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Disclosure Statement

The authors declare they have no conflicts of interest regarding the publication of this article.

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