The Characteristics of Blood Pressure Variability in Stage 3 Chronic Kidney Disease Patients with Diabetic and (not or) Non-Diabetic Nephropathy

*Yuliia Klitsunova, Roman Pozdniakov, Andrey Ostapenko
*State Institution “Zaporizhia Medical Academy of Post-Graduate Education Ministry of Health of Ukraine”, Ukraine

Abstract

**background**

Hypertension (HTN) and metabolic changes of DM accelerate progression of ischemic heart disease, heart and renal failure, neurologic dysfunction, peripheral vascular diseases, which in turn causes increased risk of complications, disability and premature death. In this study we analyzed 24-hour blood pressure monitoring in patients with diabetic (DN) and nondiabetic nephropathy (NDN) to clarify features of BP profiles in these groups and identify factors that may influence on blood pressure variability in patients with diabetic nephropathy.

**Aim**

The aim of this study was to understand the relationship between circadian rhythm of blood pressure and renal function characteristics in subjects with chronic kidney disease (CKD) stage III of diabetic and non-diabetic etiology.

**Methods**

Thirty chronic kidney disease (CKD)-hypertensive patients without diabetes (NDN group) and thirty type 2 diabetic patients with overt DN (DN group) were enrolled in this study. The values of short-term BP variability were obtained from 24 h ambulatory BP monitoring (ABPM).

**Results**

Variance analysis or nonparametric analysis revealed that 24-h systolic BP variability was significantly higher and nighttime systolic BP variability of the DN group were significantly lower than those of the NDN group [(12,23±3,66) vs. (13,67±2,99) mmHg, P<0.05; (10,74±5,26) vs. (16,35±3,69) mmHg, P<0.05]. The patients with overt DN had larger 24-h diastolic pressure [(124,50±33,78) vs. (111,50±11,5) mmHg, P<0.05;], higher load pressure [(12,23±3,66) vs. (13,67±2,99) mmHg, P<0.05; (10,74±5,26) vs. (16,35±3,69) mmHg, P<0.05] and the frequency and severity of violations of the circadian rhythm of blood pressure in a lower variability and a higher magnitude and speed of morning rise in blood pressure, compared with NDN group. In the DN group, at equal rates GFR, albuminuria level and disturbances of lipid profile were significantly higher than in the group with NDN patients.

**Conclusion**

Taken together, larger short-term BP variability was detected in hypertensive type 2 diabetic patients with overt nephropathy and renal insufficiency. It may imply that the optimal BP variability level could benefit from a better glycaemic control.

List of Abbreviations
ABPM - Ambulatory Blood Pressure Monitoring;
ACE inhibitors - Angiotensin-Converting Enzyme inhibitors;
ARBs – Angiotensin II Receptor Blockers;
BP - Blood Pressure;
CKD - Chronic Kidney Disease;
DBP - Diastolic Blood Pressure;
DM – Diabetes Mellitus;
DN - Diabetic Nephropathy;
GFR – Glomerular Filtration Rate;
HTN – Hypertension;
NDN – Non-Diabetic Nephropathy;
NYHA – New York Heart Association Functional Classification;
RME - Rate of Morning Elevation;
SBP – Systolic Blood Pressure;

Keywords
24 h Ambulatory BP; Blood Pressure Variability; Diabetic Nephropathy; Glycated Hemoglobin (HbA1c); Hypertension; Glycaemic Control; Chronic Kidney Disease

Introduction
Relevance
Hypertension (HTN) is one of the main health problems that determines cardiovascular morbidity and mortality. Diabetes mellitus (DM) and hypertension are mutually aggravating diseases with damaging action against target organs: heart, kidney, vessels of brain and retina, and great arterial vessels. HTN and metabolic changes of DM accelerate progression of ischemic heart disease, heart and renal failure, neurologic dysfunction, peripheral vascular diseases, which in turn causes increased risk of complications, disability and premature death. According to some reports, prevalence of HTN in patients with DM is from 16.5 to 75%. Increasing of BP in type 2 DM in majority of the cases associated with diabetic nephropathy. One of the main types of secondary HTN in this group is parenchymal nephrogenic type. In 80% of the patients with diabetic nephropathy high BP manifests on early stage of nephropathy and appears to be one of significant causes of cardiovascular mortality in this group of patients. Diabetic nephropathy is the most important overall cause of renal failure. Furthermore, it is generally recognized, that cardiovascular diseases are the most significant causes of mortality in patients with chronic kidney diseases, including diabetic nephropathy [2], and HTN is the most important risk factor of cardiovascular disorders in patients with chronic renal disease.

It should be emphasized, that office measurements of BP are considered as least representative predictor of future cardiovascular complications in both groups of patients with and without DM [8]. But indicators of variability of blood pressure have been recognized as reliable predictors of cardiovascular events that independent from daily ranges of mean BP [9, 15]. It was shown, that variability of BP depends on activity of sympathetic nervous system and changes of arterial compliance [5, 12]. Thus, inherent properties of DM (increased activity of sympathetic nervous system, blunting of sensitivity of baro receptors, and increased arterial stiffness) contribute variability of BP, thereby burdening the damage to target organs [10, 13], and increase frequency and severity of cardiovascular events [10].

However, until now the daily variability of blood pressure in patients with diabetic nephropathy have been studied insufficiently. In this study we analyzed 24-hour blood pressure monitoring in patients with diabetic (DN)
and nondiabetic nephropathy (NDN) to clarify features of BP profiles in these groups and identify factors that may influence on blood pressure variability in patients with diabetic nephropathy.

**Purpose**

To evaluate and compare relationship between daily rhythm of BP and indicators of renal function in patients with diabetic and nondiabetic nephropathy on stage 3 of chronic kidney disease.

**Objectives of the Study**

1. To study the features of the daily profile of BP in patients with diabetic and nondiabetic stage 3 chronic kidney disease.

2. To determine factors with greatest influence on daily changes of blood pressure in patients with stage 3 chronic kidney disease of diabetic and nondiabetic etiology.

**Materials and Methods**

The study included patients aged ≥18 years with 1-2 stages of HTN diagnosed in a hospital based on criteria of hypertension according to the recommendations of the Ukrainian Association of Cardiologists (2012) and clinical recommendations of the European Society of Hypertension (2013) and stage 3 CKD both diabetic and nondiabetic etiology (according to the NKF K/DOQI classification, 2002 and the classification of the Ukrainian Association of Nephrologists (2011), functional conditions of the kidneys were assessed with glomerular filtration rate by the formula CKD-EPI, as well as the ratio of albumin-to-creatinine in urine). A total of 60 patients were examined: 30 patients with diabetic nephropathy and 30 CKD patients with non-diabetic etiology (24 patients with chronic glomerulonephritis, 6 patients with chronic pyelonephritis). The average age of the patients was 48.6 ± 5.1 years. Diurnal blood pressure monitoring was performed with the apparatus BAT41-2 using oscillometric method during 24 hours with an interval of 15-30 min day/night. All patients were instructed to record the timing of falling asleep, morning awakening and other activities in their personal diaries. The values of “daytime” and “nightime” blood pressure and pulse rates in patients were fixed according to the time of wake and sleep noted in the diaries. Patients with more than 20% of errors in measurements of BP or lack of values of BP more than 2 hours in a row were subject to repeated monitoring over the next 24 hours. Systolic blood pressure > 240 or <70 mm Hg as well as diastolic blood pressure > 150 or <40 mm Hg were removed from the profile as technical artifacts.

Exclusion criteria: patients who undergo dialysis or patients after kidney transplant achievement, patients with clinically significant heart disease (heart failure stage III-IV according to NYHA, hypertension III, myocardial infarction), stroke, stenosis of renal arteries, hepatic dysfunction, pheochromocytoma, thyrotoxicosis, and hyperaldosteronism.

All patients with diabetic nephropathy received standard therapy as a combination of metformin and glimepiride / glibenclamide in addition to the diet (diet # 9) and regiment of physical activity. Treatment of hypertension, according to the recommendations of the Ukrainian Association of Cardiologists, included α- and β-blockers, ACE inhibitors or ARBs, calcium channel blockers, diuretics. Clinical examination of patients included collection of complaints and history, physical examination, biochemical and instrumental tests.

According to the level of glycated hemoglobin (HbA1c) patients with diabetic nephropathy were divided into 2 subgroups: 1 group (HbA1c <7%) and 2 group (HbA1c ≥7%).

Statistical processing of data was carried out using the software package Statistica 6.0 for Windows. The value of the indicators: median (Mdn), 25% is lower quartile, 75% is upper quartile (Mdn [25%, 75%]). Statistical differences were determined at a significance level of p <0.05. To compare the values in two groups, the Mann-Whitney U test was used for unrelated samples and the Wilcoxon criterion for related samples.

**Results and Discussion**

As a result of the study, in the group of patients with diabetic nephropathy a significant occurrence of patients with “non-dipper” (25 patients) and “night-peaker” types (3 patients) was found in comparison with the group of patients with nondiabetic nephropathy (21 and 0 respectively). In the diabetic group the level of albumin-to-creatinine in the urine was significantly higher than in the group of patients with nondiabetic nephropathy (4.08 ± 6.15 mg/g and 1.43 ± 2.94 mg/g, respectively). Also, in the group of patients with diabetic nephropathy, a significantly higher level of triglycerides was found in comparison with the group of nondiabetic nephropathy (2.72 ± 1.53 mmol/L and 1.55 ± 1.14 mmol/L, respectively).

It is important to note, that during 24-h monitoring...
reliable differences of BP were mostly in diastolic values. Thus, the level of mean daily DBP in the group of patients with diabetic nephropathy was significantly higher than in the group of nondiabetic nephropathy (124.50 ± 33.78 mm Hg and 111.50 ± 11.5 mm Hg, respectively). Interestingly, that in patients with non-diabetic nephropathy, there was a tendency to decline of blood pressure in the morning (versus its elevation in normal physiology). Thereby, pattern of systolic and diastolic BP changes in this group of patients has a negative value: SBP (-54.88 ± 21.35) mmHg and DBP (-70.88 ± 14.35) mm Hg respectively. In patients with diabetic nephropathy, these parameters exceed the norm (SBP (66.02 ± 21.48) mm Hg and DBP (57.13 ± 12.75) mm Hg). However, these values are not sufficiently informative for patients with a monotonous daily BP profile. A more complete characteristic yields conjoint analysis of rate of morning elevation (RME) and magnitude of morning elevation of BP. Since RME is independent from daily variability, absolute values of BP and timing (rising occurs not always in the morning hours), this integral index can give us better understanding of daily BP fluctuations in both groups. In DN group values of RME for systolic and diastolic BP are (54.83 ± 2.48) mm Hg/hour and (10.83 ± 2.69) mm Hg/hour. For NDN they are: SBP (24.86 ± 2.36) mm Hg/hour and DBP (29.61 ± 8.24) mm Hg/hour. These differences of RME were statistically significant.

Mentioned phenomenon has great clinical importance, as in the period from 6:00 a.m. to 12:00 a.m. there is an abrupt rising of blood pressure, an increase in vascular tone, which coincide with neurohumoral changes (activation of sympathoadrenal and renin-angiotensin-aldosterone systems, reduction of parasympathetic activity), increase in platelet aggregation, hypercoagulability, and decrease in fibrinolytic activity. Elevation of blood pressure in the morning, combined with neurohumoral changes, can be a trigger for a cascade of well-known processes contributing to cardiovascular complications. Also higher magnitude and rate of elevation of BP in early morning hours appears to be an independent risk factor for hypertrophy of left ventricle.

In addition, in the group of patients with diabetic nephropathy the values of the night variability of SBP were significantly lower than in the group of patients with nondiabetic nephropathy (13.67 ± 2.99) mm Hg and (16.35 ± 3.69) mm Hg, respectively.

Conclusions
1. In patients with diabetic nephropathy identified tendency of developing increased diastolic blood pressure.
2. It has been shown, that with a comparable decline of renal function, hypertension in diabetic nephropathy differs from hypertension in nondiabetic nephropathy by higher values of load pressures, and frequency and severity of disturbances of circadian rhythm of BP with lower variability values and higher magnitude and morning elevation rates.
3. With equal GFR, in patients with diabetic nephropathy the level of albuminuria is significantly higher than in the group of patients with nondiabetic renal impairment.
4. Patients with diabetic nephropathy have more pronounced disturbances of lipid profile.
5. Taken together, larger short-term BP variability was detected in hypertensive type 2 diabetic patients with overt nephropathy and renal insufficiency. It may imply that the optimal BP variability level could benefit from a better glycaemic control.

Discussion
Age, BMI, serum urea nitrogen, eGFR, albumin/creatinine ratio, and some lipid metabolic indicators have effects on BP variability as it was shown in many studies [9-10, 12, 14], but they are not specific and cannot explain the differences between the DN group and NDN group or the differences between subgroups with different HbA1c levels when all of the data from these indicators showed no statistical difference. Subsequent studies of populations [3] and hypertensive cohorts generally corroborated that a raised nocturnal BP predicted a higher rate of cardiovascular complications especially in patients with DN [14]. Despite the apparent agreement between these previously published large-scale studies [11] several potential limitations warranted further clarification of the prognostic accuracy of the day vs. night ambulatory BP. Many studies considered only fatal outcomes [15] or did not have the power to study cause-specific cardiovascular end points [9, 15]. BP is considered physiologically regulated by various complex factors (e.g., environmental stimulation, genetic factors, autonomic nervous system, augmentation of the renin-angiotensin-aldosterone system (RAS), vascular function, ageing,
long-term smoking, excessive drinking, obesity, caloric over-loading, emotions, inflammation, and cardiovascular control). However, the interrelationships between these factors for hypertension and BP variability are, at best, complex and are not yet well-defined.

**Reference**


### Table 1: Clinical and laboratory findings in patients with stage 3 diabetic and nondiabetic CKD

<table>
<thead>
<tr>
<th>Index</th>
<th>Diabetic nephropathy</th>
<th>Nondiabetic nephropathy</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>30</td>
<td>30</td>
<td>nr</td>
</tr>
<tr>
<td>Age</td>
<td>61.58±6.14</td>
<td>58.68±12.75</td>
<td>nr</td>
</tr>
<tr>
<td>Gender (men/women)</td>
<td>18/12</td>
<td>20/10</td>
<td>nr</td>
</tr>
<tr>
<td>Smoking status</td>
<td>22 (36.8%)</td>
<td>16 (31.4)</td>
<td>nr</td>
</tr>
<tr>
<td>Duration of diabetes (months)</td>
<td>114</td>
<td></td>
<td>nr</td>
</tr>
<tr>
<td>Duration of hypertension (month)</td>
<td>102</td>
<td>124</td>
<td>nr</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>19 (63.3%)</td>
<td>23 (76.7%)</td>
<td>nr</td>
</tr>
<tr>
<td>ACEI &amp; ARB</td>
<td>16 (53.3%)</td>
<td>11 (36.7%)</td>
<td>nr</td>
</tr>
<tr>
<td>α-Blocker</td>
<td>9 (30%)</td>
<td>9 (30%)</td>
<td>nr</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>7 (23.3%)</td>
<td>10(33.3%)</td>
<td>nr</td>
</tr>
<tr>
<td>Diuretics</td>
<td>4 (13.3%)</td>
<td>1 (3.3%)</td>
<td>nr</td>
</tr>
</tbody>
</table>

### Table 2: Comparison of DN patients with different levels of HbA1c

<table>
<thead>
<tr>
<th>Index</th>
<th>Group A (HbA1c&lt;7%)</th>
<th>Group B (HbA1c≥7%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variability of SBP for 24 h, mm Hg</td>
<td>11.75±2.98</td>
<td>12.01±4.22</td>
<td>ns</td>
</tr>
<tr>
<td>Variability of DBP for 24 h, mm Hg</td>
<td>6.85 (2.51)</td>
<td>8.55 (2.99)</td>
<td>ns</td>
</tr>
<tr>
<td>Daytime variability of SBP, mm Hg</td>
<td>19.02 (3.33)</td>
<td>26.30 (5.76)</td>
<td>0.005</td>
</tr>
<tr>
<td>Daytime variability of DBP, mm Hg</td>
<td>12.63 (1.61)</td>
<td>18.72±2.29</td>
<td>0.005</td>
</tr>
<tr>
<td>Nighttime variability of SBP, mm Hg</td>
<td>10.27 (5.69)</td>
<td>14.86±4.13</td>
<td>0.005</td>
</tr>
<tr>
<td>Nighttime variability of DBP, mm Hg</td>
<td>10.87 (5.98)</td>
<td>13.25 (4.79)</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 31: 1281-1357.


