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PULSE PRESSURE IS MORE RELEVANT THAN SYSTOLIC AND DIASTOLIC BLOOD PRESSURE IN PATIENTS WITH TYPE 2 DIABETES AND CARDIOVASCULAR DISEASE

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Abstract

Background and aims. *The parameters evaluated during 24-hour ambulatory blood pressure monitoring were reported to be predictors of cardiovascular events. We aimed to investigate mean blood pressure, blood pressure variability and pulse pressure during 24-hour ambulatory blood pressure monitoring in type 2 diabetes patients and to establish their relationship with the presence of atherosclerotic cardiovascular disease (CVD).*

Methods. *The observational study included type 2 diabetes patients randomly selected and distributed in 2 study groups depending on the presence of atherosclerotic cardiovascular disease: CVD(-), n=90, and CVD(+), n=87. Daytime, nighttime and 24-hour systolic and diastolic blood pressure were monitored and mean blood pressure, blood pressure variability and pulse pressure were calculated.*

Results. *The study groups were comparable as age, gender ratio, smoking status, body mass index and abdominal circumference. Diabetes and hypertension duration were significantly higher in the CVD(+) group. Mean systolic and diastolic blood pressure, blood variability, dipper prevalence did not differ between study groups. Pulse pressure was significantly higher in the CVD(+) group compared to CVD(-) group (daytime pulse pressure 56.2±13.1 vs. 50.6±11.3 mmHg, p=0.003; nighttime pulse pressure 56.5±14.2 vs. 50.7±12.4 mmHg, p=0.005; 24-hour pulse pressure 54.7±13.6 vs. 49.0±12.0 mmHg, p=0.003).*

Conclusions. *Ambulatory pulse pressure was significantly higher in patients with type 2 diabetes and atherosclerotic cardiovascular disease compared to those without cardiovascular disease, although mean systolic and diastolic blood pressure and blood pressure variability were similar.*

Keywords: diabetes mellitus, cardiovascular disease, ambulatory blood pressure monitoring, pulse pressure

Background and aims

It is well known from a number of large randomized controlled trials that arterial blood pressure (BP) is a very important determinant of cardiovascular risk [1]. The results of the United Kingdom Prospective Diabetes Study (UKPDS) have demonstrated the importance of systolic BP as a risk factor for cardiovascular events [2]. Pulse pressure (PP) is defined as the difference between systolic and diastolic BP and it is dependent on arterial wall elastic properties [3]. The Framingham Heart Study demonstrated that PP was the strongest predictor of coronary heart disease risk in individuals older than 50 years of age [4], although a meta-analysis suggests that systolic BP may be more predictive than PP [5]. A recent meta-analysis found an increase of 10 mmHg in PP to be positively associated with the risk of stroke occurrence [6]. The importance of PP in determining cardiovascular risk is due to the fact that PP is a marker of large artery stiffness, an independent predictor of cardiovascular risk [7]. Evidence showing that PP is an independent predictor of atherosclerotic cardiovascular disease (CVD) have not led to a change in current guidelines that continue to focus on reducing BP

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rather than on reducing PP [8].

Evidence showed that widened PP is a powerful independent predictor of incident CVD in patients with type 2 diabetes, but there are not many studies that have investigated the predictive value of PP as a risk factor for CVD in patients with type 2 diabetes [1,9,10]. Some studies showed that PP was higher in type 2 diabetes patients than in non-diabetic patients, and PP was positively associated with cardiovascular mortality in type 2 diabetes patients [11]. Also, PP was associated with micro- and macrovascular complications of type 2 diabetes. This association can be explained by the fact that type 2 diabetes is associated with premature arterial stiffening. As the large arteries stiffen, systolic BP increases as a consequence; but diastolic BP actually falls, leading to the increase in PP [1,12].

Office BP measurement can be easily used to evaluate hypertension control. However, 24-hour ambulatory blood pressure monitoring (ABPM) provides information on circadian changes in BP and can estimate mean BP, BP variability, PP and many other parameters derived from BP [13]. Also, 24-hour ABPM correlates better with cardiovascular outcome than clinic BP levels do [14]. Given this data, we aimed to investigate mean BP, BP variability and PP evaluated during 24-hour ABPM in type 2 diabetes patients and to establish their relationship with the presence of atherosclerotic CVD.

Methods

Patients

The observational study included type 2 diabetes patients randomly selected from the Clinical Centre of Diabetes, Nutrition and Metabolic Diseases in Cluj-Napoca, Romania, between July 2013 and February 2014. The patients were distributed into two study groups depending on the presence of atherosclerotic cardiovascular disease: absent CVD(-), n=90, and present CVD(+), n=87. Patients were not included if they had been previously diagnosed with unstable cardiovascular disease, secondary hypertension, inflammatory diseases, malignancies, renal or hepatic failure. Atherosclerotic cardiovascular disease was defined as the presence of coronary heart disease, peripheral arterial disease or cerebrovascular disease presumed to be of atherosclerotic origin [15].

In accordance with the World Medical Association Declaration of Helsinki revised in 2000, Edinburgh, and institutional guidelines, the protocol was approved by the local Ethics Committee of the Iuliu Haţieganu University of Medicine and Pharmacy Cluj-Napoca, Romania. All patients were aware of the investigational nature of the study and provided written informed consent before any study procedure.

Study protocol

The study protocol was described in a previous paper [16].

24-hours ambulatory blood pressure monitoring

The 24-hour ABPM technique was previously described [16]. Mean BP, BP variability and PP were calculated during daytime, nighttime and 24-hour periods. BP variability was estimated as standard deviation of mean BP [17]. PP was calculated as the difference between systolic and diastolic BP [11].

Statistical analysis

Data analysis was performed using the R 2.15.1 software for Windows. Kolmogorov–Smirnov test was used to test the normal distribution of all continuous variables. Data were expressed as mean ± standard deviation or median and 25th and 75th percentiles, or numbers and percentages. ANOVA test was used to compare the groups' parametric variables. Chi-square test was applied in order to verify the differences in frequency for nominal variables between the groups. A value of $p<0.05$ was considered statistically significant.

Results

Characteristics of the study groups

The characteristics of the study participants are presented in Table I.

Table I. Baseline characteristics of the study groups.

Variables	CVD(-) group (n=90)	CVD(+) group (n=87)	*p-value*
Age (years)	59.7±7.1	61.3±7.2	0.152
Male gender n, (%)	41 (45.6)	33 (37.9)	0.307
Smoking status n, (%)	19 (21.1)	14 (16.1)	0.430
Diabetes duration (years)	8.2±7.5	12.5±8.5	0.001
Hypertension duration (years)	6.4±5.8	11.1±6.6	<0.001
Systolic BP at admission (mmHg)	139.6±20.9	142.5±19.5	0.336
Diastolic BP at admission (mmHg)	82.3±10.7	79.8±11.0	0.108
Heart rate at admission (beats/minute)	78.1±14.3	77.2±14.0	0.664
Body mass index (kg/m2)	31.5±5.0	32.2±4.9	0.317
Waist circumference (cm)	107.2±11.9	109.5±11.9	0.208
Total cholesterol (mg/dl)	198.6±51.2	182.7±55.1	0.048
HDL-cholesterol (mg/dl)	42.9±12.4	40.2±11.3	0.134
Triglycerides (mg/dl)	170.5 (123.0; 271.8)	181.0 (116.0; 255.0)	0.923
LDL-cholesterol (mg/dl)	109.2 (86.7; 135.4)	96.4 (71.8; 121.8)	0.042

Values are means +/− standard deviation or median and 25th and 75th percentiles or numbers and percentages. CVD, atherosclerotic cardiovascular disease; BP, blood pressure.

We found no significant differences in age, gender, smoking status, systolic and diastolic BP at admission, heart rate at admission, body mass index and waist circumference between the two study groups. Significantly higher durations of diabetes and hypertension were observed in the CVD(+) group. Dyslipidemia was present in 82 patients (91.1%) from CVD(-) group and in 84 patients (96.6%) from CVD(+) group. Total cholesterol was significantly higher, while LDL-cholesterol was significantly higher in the CVD(-) group compared to CVD(+) group; there were no significant differences in HDL-cholesterol and triglycerides levels between study groups.

The patients included in the CVD(+) group presented one or more manifestations of atherosclerotic CVD in different percentages. Most patients (n=75, 86.2%) were diagnosed with ischemic heart disease (including previous myocardial infarction), while history of stroke (n=21, 24.1%), and peripheral arterial disease (n=19, 21.8 %) were present in lower numbers of patients. Each patient could have had multiple localization of atherosclerosis.

24-hours ambulatory blood pressure monitoring

When analyzing 24-hour ABPM parameters, we observed that mean systolic and diastolic BP during the daytime, nighttime and 24-hour periods were higher in the type 2 diabetes CVD(+) group compared to the type 2 diabetes CVD(-) group, but the difference did not reach statistical significance (Table II). Systolic and diastolic BP at admission were statistically significantly higher than ambulatory systolic and diastolic BP monitored during daytime, nighttime and 24-hour periods ($p<0.001$).

We found higher systolic BP variability and lower diastolic BP variability in the type 2 diabetes CVD(+) group compared to type 2 CVD(-) group, without reaching statistical significance (Table III).

PP, calculated as the difference between systolic BP and diastolic BP, was statistically significantly higher during daytime, nighttime and 24-hour periods in the type 2 diabetes CVD(+) group compared to type 2 diabetes CVD(-) group, as can be seen in Table IV. Also, PP at admission was statistically significantly higher in the type 2 diabetes CVD(+) group compared to type 2 diabetes CVD(-) group. When comparing PP at admission with daytime PP ($p<0.001$), nighttime PP ($p<0.001$) and 24-hour PP ($p<0.001$), we found statistically significantly higher values of PP at admission.

Table II. Mean systolic and diastolic blood pressure during 24-hours ambulatory blood pressure monitoring in the study groups.

Variables	CVD(-) group (n=90)	CVD(+) group (n=87)	p-value
Daytime mean systolic BP (mmHg)	129.5±14.3	133.4±13.7	0.064
Nighttime mean systolic BP (mmHg)	123.2±17.0	127.4±16.1	0.092
24-hour mean systolic BP (mmHg)	126.3±15.1	130.4±14.2	0.066
Daytime mean diastolic BP (mmHg)	78.9±10.1	77.2±8.9	0.242
Nighttime mean diastolic BP (mmHg)	72.4±10.7	71.0±9.7	0.335
24-hour mean diastolic BP (mmHg)	77.4±9.9	75.7±8.8	0.246

Values are means +/− standard deviation; CVD, atherosclerotic cardiovascular disease; BP, blood pressure.

Table III. Systolic and diastolic blood pressure variability during 24-hour ambulatory blood pressure monitoring in the study groups.

Variables	CVD(-) group (n=90)	CVD(+) group (n=87)	p-value
Daytime systolic BP variability (mmHg)	10.5±3.4	10.9±4.0	0.547
Nighttime systolic BP variability (mmHg)	9.5±3.6	10.3±4.2	0.170
24-hour systolic BP variability (mmHg)	11.1±3.3	11.6±3.9	0.329
Daytime diastolic BP variability (mmHg)	8.0±2.1	7.6±2.5	0.241
Nighttime diastolic BP variability (mmHg)	7.4±2.4	7.4±2.2	0.943
24-hour diastolic BP variability (mmHg)	8.6±2.0	8.3±2.3	0.296

Values are means +/− standard deviation. CVD, atherosclerotic cardiovascular disease; BP, blood pressure.

Table IV. Pulse pressure during 24-hours ambulatory blood pressure monitoring in the study groups.

Variables	CVD(-) group (n=90)	CVD(+) group (n=87)	p-value
Daytime pulse pressure (mmHg)	50.6±11.3	56.2±13.1	0.003
Nighttime pulse pressure (mmHg)	50.7±12.4	56.5±14.2	0.005
24-hour pulse pressure (mmHg)	49.0±12.0	54.7±13.6	0.003
Pulse pressure at admission (mmHg)	57.1±15.1	62.7±15.5	0.016

Values are means +/− standard deviation or numbers and percentages CVD, atherosclerotic cardiovascular disease.

Table V. Blood pressure control according to the European Society of Hypertension and European Society of Cardiology recommendations of 2013.

Variables	CVD(-) group (n=90)	CVD(+) group (n=87)	p-value
Daytime BP control (<135/85mmHg)	51 (56.7%)	41 (47.1%)	0.206
Nighttime BP control (<120/70mmHg)	38 (42.2%)	30 (34.5%)	0.293
24-hour BP control (<130/80mmHg)	38 (42.2%)	35 (40.2%)	0.789

Values are means +/− standard deviation or numbers and percentages. CVD, atherosclerotic cardiovascular disease; BP, blood pressure.

Regarding the distribution of patients in the two study groups according to dipper or non-dipper status, we found that 18% of patients in the CVD(+) group were dippers compared to 16% of patients in the CVD(-) group. There was no evidence of a correlation between the dipping index and the presence of CVD (p= 0.625).

BP control as recommended by hypertension guideline published by European Society of Hypertension and European Society of Cardiology in year 2013 [8], was less satisfactory in the CVD(+) group than in the CVD(-) group during the daytime, nighttime and 24-hour periods, although the results did not reach statistical significance (Table V).

Discussion

The most important observation of our study was that ambulatory PP was statistically significantly higher during daytime, nighttime and 24-hour periods in patients with type 2 diabetes and atherosclerotic cardiovascular disease compared to patients with type 2 diabetes without atherosclerotic cardiovascular disease, while the mean systolic and diastolic BP, as well as BP variability during daytime, nighttime and 24-hour were comparable between the two groups. This demonstrates that ambulatory PP was more relevant than mean BP and BP variability in patients with type 2 diabetes and atherosclerotic cardiovascular disease. Our finding is in agreement with other studies [1,7,18], although there are results that suggest that PP is much less informative than systolic and diastolic BP [5], but these results do not refer to ambulatory PP. Other evidence suggests that the magnitude of association between mean BP, PP and CVD is similar among these BP indices [19]. Therefore, the assessment of PP may assist in risk stratification and monitoring therapeutic response [1] and if PP is lowered a marked cardiovascular risk reduction could to be achieved [7]. However, systolic BP cannot be replaced with brachial artery PP as a single measure of cardiovascular risk [19]. Thus, the assessment of risk in diabetes patients should begin with measuring the increase in systolic BP and then continue with stratifying the risk according to the PP range [20]. ABPM has been described in literature as a strong predictor of cardiovascular morbidity [21], being independently associated with future cardiovascular events in patients with type 2 diabetes [22]. The importance of ABPM over 24 hours was also demonstrated by our study, with the obtained parameters being more relevant than the isolated values of BP measured in the medical office. The best example is represented by the results obtained in the 24-hour ambulatory PP evaluation, as described above.

Even though mean systolic BP during daytime, nighttime and over 24 hour periods was higher in the diabetes CVD(+) group compared to the CVD(-) group, these results did not reach statistical significance. Conversely, diastolic BP values were non-significantly lower in the CVD(+) group compared to the CVD(+) group. These results confirm the need for 24 hour ABPM and PP measurement in patients with type 2 and CVD. Similarly, it was observed that systolic BP variability was non-significantly higher in the diabetes CVD(+) group, while diastolic BP variability was non-significantly lower in the diabetes CVD(+) group compared to diabetes CVD(-) group. BP variability was described as a risk factor for cardiovascular events and was directly correlated with subclinical inflammation [16,23] and subclinical myocardial function [24]. However, as in the case of mean systolic and diastolic BP, BP variability was similar in the two groups, highlighting the relevance of PP measurement in patients with type 2 diabetes and CVD.

Also, we found that PP at admission was statistically significantly higher than 24-hour ambulatory PP, while mean systolic and diastolic BP were statistically significantly higher than mean BP during daytime, nighttime and 24-hour periods. Our results indicating the presence of white-coat hypertension in the study population are confirmed by a previous study reporting that increased PP in the clinic is positively associated with the presence of white-coat hypertension [25]. White-coat hypertension is a benign condition; moreover, it seems that patients with white-coat hypertension are frequently treated for high office BP, and thus, lower BP might be responsible for lower incidence of cardiovascular events [26]. The opposite condition, that we might have expected to find in our study, is masked hypertension, which predisposes to cardiovascular events, particularly in the presence of diabetes and obesity. Since 24-hour ABPM remains the gold standard for diagnosing masked and white coat hypertension, it is important to consider it for effective diagnosis and control of hypertension, regardless the presence of atherosclerotic CVD [27].

Non-dippers are defined as patients with an overnight mean BP reduction less than 10% of mean

daytime BP. Many reports say that non-dippers have an increased risk for cardiovascular or cerebrovascular disease [28]. We would have expected the proportion of patients with non-dipper status to be higher among patients with present CVD. Instead, the percentage was higher in those without CVD (74% vs. 69%), but the results were not statistically significant. A possible explanation would be the time of day when the antihypertensive medication was administered. It has been reported that the administration of antihypertensive medication during the evening was associated with higher prevalence of dipper profile [29].

It is well known that older adults with diabetes have a higher risk for developing atherosclerotic CVD than young adults with diabetes and elderly adults without diabetes [30]. The results obtained in this study confirm these data, the group of patients with CVD(+) had a longer duration of diabetes compared to those without CVD, a statistically significant result. It has also been confirmed by this study that hypertension is a risk factor for CVD, the duration of the hypertension being significantly longer in the diabetes CVD(+) group, as the groups were comparable in age and gender distribution.

The presence of obesity and increased abdominal circumference was observed in both study groups. Previous studies have shown that obesity was associated with increased aortic stiffness, ambulatory systolic BP [31] and PP [32], thus, interfering with atherosclerosis [33]. Although the positive relationship between blood lipid and pulse pressure was reported [34], we did not found a significant association.

Most patients with type 2 diabetes who had atherosclerotic cardiovascular disease were diagnosed with ischemic heart disease (86.2%); much smaller percentages presented other clinical manifestation of atherosclerotic cardiovascular disease. This is probably due to the predilection of atherosclerosis in the coronary arteries in patients with diabetes [35].

Conclusions

We found that ambulatory pulse pressure was significantly higher in patients with type 2 diabetes and atherosclerotic cardiovascular disease compared to type 2 diabetes without atherosclerotic cardiovascular disease, although mean systolic and diastolic blood pressure and blood pressure variability were similar. Our results suggest that pulse pressure might be more relevant to cardiovascular disease risk than mean blood pressure and blood pressure variability in type 2 diabetes patients. Also, our findings emphasize the importance of 24-hour ambulatory pulse pressure monitoring in type 2 diabetes.

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