

# Ambulatory Blood Pressure Monitoring in Diabetic Hypertensive Patients, Single Center Report – Preliminary Results

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## ABSTRACT

*ABPM (ambulatory blood pressure monitoring) has been considered to be a useful tool for the diagnosis and management of arterial hypertension and is a better predictor of future cardiovascular events as compared with conventional office-based BP measurements. Despite its potential values, ABPM is not yet widely used in many clinical offices mainly because of lack of knowledge and unavailability. Aims of this preliminary study are to determine the control of hypertension and circadian BP characteristics in patients referred to our Centre whom we enrolled in the »HRKMAT« Study-Croatian Registry of ABPM. Although patients included in HRKMAT Study had other risk factors for cardiovascular diseases, in this paper we analyzed differences between hypertensive diabetics (N=20) and nondiabetics (N=57). 24-hours ABPM was performed with an automated oscillometric device Mobil-O-Graph NG Vers.20 and office BP using mercury sphygmomanometer. Average office BP was 139/90 mmHg, and average 24h ABPM was 130/82 mmHg. Majority of hypertensive patients used antihypertensive drugs (79.2%). Diabetic patients had higher systolic BP but lower diastolic BP. There were no statistically significant differences in dipping status, but earlier BP surge was noticed in reverse diabetic dippers than in reverse non-diabetic dippers. Though no significant, there was higher prevalence of WCH (»white coat hypertension«) in diabetics, and we found MH (masked hypertension) in only two patients. These are preliminary results on ABPM from our centre and of HRKMAT registry. Further and more valuable data and results are awaited from the main HRKMAT database.*

**Key words:** hypertension, ambulatory blood pressure monitoring, circadian blood pressure pattern, diabetes mellitus

## Introduction

According to international guidelines, ambulatory BP monitoring (ABPM) has been established as an important instrument in the diagnosis and management of hypertension.<sup>1,2</sup> It gives the opportunity to evaluate 24-hour average blood pressure (BP); daytime (awake) BP; night-time (asleep) BP; systolic and diastolic blood pressure load; nocturnal dipping of the BP, BP variability, morning BP surge, and particular conditions such as white-coat hypertension (WCH) and masked hypertension (MH).<sup>3</sup> Moreover, ABPM offers more accurate prognostic information of cardiovascular outcomes than office BP readings.<sup>4</sup> Hypertension coexisting with diabetes and obesity has a major impact on cardiovascular prognosis. Many trials have emphasized the need for tight blood pressure control in patients with diabetes mellitus, but ACCORD

trial proved that aggressive BP control, targeting systolic BP of less than 120 mmHg, as compared with less than 140 mm Hg, did not reduce the rate of composite outcomes of major cardiovascular events.<sup>5,6</sup> Therefore, individualized control of BP is becoming more important, especially in patients with diabetes. Abnormal patterns of circadian blood pressure variation, evaluated by ambulatory blood pressure monitoring, predict cardiovascular prognosis in diabetic patients.<sup>7</sup> Some studies showed that ambulatory BP control is more closely associated with target organ damage of the brain, heart, and kidney, even more than glycemic control, thereby ambulatory BP control could be effective in preventing future risk of cardiovascular disease in patients with diabetes.<sup>7</sup>

## Methods

This is a preliminary study in the framework of the »HRKMAT« Study, an national registry of ABPM that was organized and conducted by the Croatian Society of Hypertension. The main aim was to determine hypertension control and overall cardiovascular and renal risks in daily clinical practice in Croatia. The protocol of Study has been reviewed by the appropriate ethics committee and therefore been performed in accordance with the ethical standards. All patients gave their informed consent prior to inclusion in the study. We retrospectively evaluated ABPM recordings from 120 patients performed with an automatic oscillometric device. Inclusion criteria were men and women aged >18 years, mainly referred to our Centre because of previously diagnosed hypertension on the basis of an office BP >140/90 mmHg. Exclusion criteria were pregnancy, arterial fibrillation or other cardiac arrhythmias which might make unreliable the automatic blood pressure measurement with the oscillometric technique and upper arm circumference <22 cm. At the time of visit, evaluation of medical history and physical examination were performed. BP was obtained at the office with a calibrated mercury sphygmomanometer after 5-minute rest in a sitting position with a standard cuff (23 x 12 cm) or large cuff (34 x 15 cm) applied around patient's non-dominant arm. The first and fifth Korotkoff's sounds were taken as the systolic and diastolic BPs. Hypertension was defined as systolic BP  $\geq$ 140/90 mmHg and/or taking antihypertensive drugs. Thereafter, 24-hour ABPM was performed on each patient's non-dominant arm using a Mobil-O-Graph NG Vers.20 automated noninvasive oscillometric devices. The accuracy of the device was checked against the standard auscultatory method to ensure that the difference in BP measurements between methods did not exceed 5 mmHg. SBP, DBP and HF were recorded every 20 minutes throughout the day and every 30 minutes at night. Daytime period was predefined from 7 a.m. until 10 p.m. and night-time period was from 10 p.m. until 7 a.m. Each ABPM monitoring dataset was automatically scanned to remove artificial readings to preselected criteria. Data was edited by omitting all readings of zero, systolic BP readings >260 mmHg, diastolic BP >150 mmHg, all readings where the differences between the systolic and diastolic BPs were less than 10 mmHg and heart rate readings <20 or >200. Readings were evaluated if the percentage of successful readings was above 80%. ABPMs were performed on working days, and patients were instructed to maintain their usual activities, and return the following morning for device removal, and to keep their arms extended during cuff inflation. The following ABPM parameters were evaluated: mean ambulatory 24-h systolic and diastolic BP levels, mean ambulatory daytime systolic and diastolic BP levels, mean ambulatory nighttime systolic and diastolic BP levels, average blood pressure load, daytime, nighttime and 24 hours heart rates, BP variability. The circadian characteristics of BP were also automatic estimated. A normal dipping pattern was diagnosed when the reduction in average

SBP during the night period was >10% of mean SBP during the day, if the reduction was >20% the patients was classified as an extreme dipper, if it was less than 10% it was classified as non-dipper, and if mean night SBP was higher than the day one, the patients was classified as a inverter. Valid registries had to fulfill pre-established criteria, including >80% of BP successful recording, 24-hour duration and >1 BP measurement per hour.

## Statistical Analysis

To test differences between means Student's t-test and Mann-Whitney U test, as well as paired t-test and Kruskal Wallis H test for paired data, were employed for normally distributed and skewed data respectively. Chi-square test was used for categorical data.  $p \geq 0.05$  was considered statistically significant. Statistical program IBM SPSS v.19 (Chicago, IL) was used.

## Results

Out of total 120 patients, 77 patients met the including criteria. Other 43 patients were excluded mostly because of less than 80% successful readings on ABPMs, and there was one pregnant women. There were 43 (55.8%) men and 34 (44.2%) women with the mean age  $57 \pm 16$  (range 22–85 years). In 93.4% (n=71) patients diagnoses of hypertension was established before, and 26% (n=20) had diabetes mellitus typ 2 as well. Mean BMI was  $27.7 \pm 4.7$  kg/m<sup>2</sup> and mean waist circumference was  $98.3 \pm 15.3$  cm. Dyslipidemia and history of cardiovascular and cerebrovascular diseases were recognized in 36 (52.2%) and 18 (23.4%) patients, respectively. Family history of hypertension, diabetes, dyslipidemia and chronic kidney disease were in 68.4%, 34.2%, 25.3% and in 13.2% patients, respectively.

There were 18.2% (n=14) current smokers, 20.8% (n=16) ex-smokers, and 61% (n=47) non-smokers. Data on physical activity showed that only 22.1% (n=17) practiced mild physical activities (less than 200 minutes weekly), 6.5% (n=5) moderate (200–300 minutes weekly) and 1.3% (n=1) practiced extreme physical activity (more than 300 minutes weekly). Average office SBP/DBP values were  $139/90 \pm 30/14$  mm Hg and average 24-hour ambulatory BP values were  $130/82 \pm 15/10$  mm Hg (Table 1). In the whole populations, the prevalence of non-dippers was 54.5%. There were 36.6% nondippers, 5.6% extreme dippers and 22.5% reverse dippers for systolic BP, and 35.2% nondippers, 11.3% extreme dippers and 16.9% reverse dippers for diastolic BP. There were lower BP variability in nondippers. Considering drug treatment – 79.2% (n=61) patients had been previously treated with at least one drug. Of them 54.5% (n=42) were taking ACE-inhibitors, 14.3% (n=11) angiotensin receptor blockers, 50.6% (n=39) calcium channel antagonists, 39% diuretics, 37.7% (n=29) beta-blockers, 19.5% (n=15) moxonidine and 5.2% (n=4) urapidil.

There were more older and overweight patients in diabetic group. Dyslipidemia and family history of diabetes mellitus were also more common in diabetic group. Aver-

**TABLE 1**  
BLOOD PRESSURE VALUES IN PATIENTS DIVIDED INTO THE GROUPS OF NONDIABETICS AND DIABETICS

	Nondiabetics		Diabetics		<i>p</i>
	Mean	SD	Mean	SD	
Office SBP	138.31	30.52	140.90	29.26	0.743
Office DBP	90.42	13.37	89.15	15.21	0.727
ABPM (No)	45.63	6.97	47.35	6.39	
Mean 24h SBP (mmHg)	129.23	15.38	133.30	14.32	0.309
Mean 24h DBP (mmHg)	83.35	10.79	79.20	8.95	0.131
Mean HR (bpm)	71.65	8.42	69.75	8.55	0.395
Mean PP (mmHg)	45.77	9.13	54.10	11.07	0.002
Daytime SBP (mmHg)	131.94	14.70	137.00	13.04	0.182
Daytime DBP (mmHg)	85.69	10.46	82.15	8.21	0.178
Daytime HR (bpm)	75.15	9.46	74.20	9.49	0.703
Daytime PP (mmHg)	46.26	9.46	54.90	11.11	0.002
Nighttime SBP (mmHg)	123.58	18.60	126.10	18.99	0.610
Nighttime DBP (mmHg)	78.69	13.13	73.50	11.71	0.126
Nighttime HR (bpm)	76.71	89.60	58.65	16.27	0.375
Nighttime PP (mmHg)	44.82	9.77	52.80	11.95	0.005
Daytime SBP load (%)	32.39	29.15	39.75	28.01	0.337
Daytime DBP load (%)	37.61	28.37	26.15	23.21	0.113
Nighttime SBP load (%)	41.94	39.39	45.10	34.40	0.754
Nighttime DBP load (%)	46.04	35.49	35.15	34.57	0.246
BP morning surge (time)	3:36		4:50		0.029
WCH (%)	44.2		50		0.660

ABPM – ambulatory blood pressure, SBP – systolic blood pressure, DBP – diastolic blood pressure, HR – heart rate, PP – pulse pressure, BP – blood pressure, WCH – white coat hypertension, SD – standard deviation, No – number of measurements, *p* – *p*-value, bpm – beats per minute

age office-BP values were higher than average ABPMs in 50% diabetics and 44.2% nondiabetics. Diabetic patients had higher systolic and slightly lower diastolic BP values that gave result in higher pulse pressure in those patients (45.8±9.1 mm Hg vs. 54.1±11 mm Hg;  $t=3.266$ ,  $p=0.002$ ). In the group of reverse dippers, diabetic patients had statistically significant earlier BP morning surge, average around 3:36 a.m. versus nondiabetics with average BP morning surge around 4:50 a.m. ( $t=2.246$ ,  $p=0.029$ ). There were no differences in dipping status and BP values between diabetics and nondiabetics. In diabetic patients higher blood pressure load (percentage of BP measurements higher than previously defined values: 24 hours and daytime  $\geq 140/90$  mm Hg and nighttime  $\geq 120/80$  mm Hg) more than 40% was found for both systolic and diastolic BP values during the night-time period. Significant difference in several drug classes were observed between diabetics and non-diabetics, thus both ACE inhibitors and CC antagonists were used much more frequently in diabetic group. We failed to find difference in usage of diuretics between the two groups ( $p>0.05$ ). Data on ABPM values and some characteristics are shown in Table 1 and Table 2.

## Discussion

In this preliminary study we evaluated clinical conditions and BP characteristics estimated by ABPM among hypertensive patients enrolled into the HRKMAT registry in our outpatient clinic. We found that most of our patients, beside hypertension and diabetes, have also other risk factors (dyslipidemia, overweight or even obesity, age, family history of hypertension, diabetes or CV diseases, smoking and sedentary lifestyle) which altogether further increase cardiovascular risk. Dyslipidemia and family history of diabetes were more prevalent in diabetic group. Average office BP levels were slightly higher than average 24-hour ABPM levels that was an expected difference.<sup>8,9</sup> The vast majority of our patients had been previously treated with at least one antihypertensive, ACE and CC antagonists being the most represented drugs (Table 2). There were no significant differences in the average BP values between diabetics and nondiabetics, but we found slightly higher systolic and slightly lower diastolic BP among diabetic patients, that results in higher pulse pressure (PP). Nakano et al. reported that 24-h PP and nighttime SBP were independent pre-

**TABLE 2**  
CHARACTERISTICS OF ENROLLED DIABETIC AND NONDIABETICS

	Nondiabetics	Diabetics	p
Age	53.3	63.5	0.003
Gender	32/57	11/20	NS
BMI (kg/m <sup>2</sup> )	27.44±4.92	28.61±4.37	NS
Mean waist circumference (cm)	95.9±15.5	105±13	0.021
Hypertension (%)	92.9	95	NS
Dyslipidemia (%)	37.4	95	<0.001
Family history of HA (%)	71.4	60	NS
Family history of DM (%)	25.0	60	0.005
Smoking status (%)	36.8	45	NS
ACE inhibitor (%)	47.4	75	0.033
CC antagonists (%)	42.1	75	0.011
Diuretics (%)	35.1	50.0	NS

ACE – angiotensin-converting enzyme, CC – calcium channel, BMI – body mass index, DM – diabetes mellitus, HA – arterial hypertension, p – p-value, NS – no significance, Mean±standard deviation

dictors of fatal and nonfatal cardiovascular events, respectively<sup>11</sup>. Elevated PP is considered an indirect indicator of increased arterial stiffness, particularly in older individuals. Diabetic patients are thought to have increased arterial stiffness and PP, possibly due to accelerated vascular aging.<sup>11,12</sup> We found high percentage of nondippers (in total nondippers + reverse dippers) for the both systolic and diastolic blood pressure in the whole population, but we didn't find statistically significant differences between diabetic and nondiabetic group, probably because of this small sample. A blunted nighttime BP decline is regarded as a prognostic marker of cardiovascular event, both in hypertensive subjects and in the general population.<sup>13</sup> Eguchi et al. evaluated the data on the effect of risen pattern of BP on future CV events and showed that it was associated with a 150% increase in the risk of CV disease both in diabetes and essential hypertension.<sup>14</sup> In type 2 diabetes studies and meta-analysis indicate that 24 hour PP and reduced nighttime BP fall or reverse dipping predict organ damage progression, total cardiovascular events and all-cause mortality.<sup>15</sup> Abnormal patterns of circadian blood pressure variation, evaluated by ambulatory blood pressure monitoring, predict cardiovascular prognosis in diabetes mellitus.<sup>7</sup> There were high percentage of overweight and obese patients. Statistically significant higher percentage of patients with central type obesity was found in diabetics group. Some studies reported higher ABPM in patients with metabolic syndrome (MetS), but they had mostly included older individuals and those with higher office BP than those without MetS. Pooled data suggested a higher risk of nondipping status in patients with MetS.<sup>15</sup> In a study on evaluation ABPM in nondiabetic untreated hypertensives Hermida et al. found that the prevalence of nondipping status was significantly higher in patients with MetS and the single

most relevant factor in definition of MetS associated with nondipping was elevated waist circumference.<sup>16</sup>

We found blood pressure loads higher than 40% for both systolic and diastolic BP in nondiabetics, and for systolic in diabetics. Blood pressure load elevation is associated with the development of target-organ damage and higher cardiovascular risk, especially when daytime BP is higher than normal in 40% readings, even in mild hypertension, and therefore it should be treated earlier.<sup>17–20</sup>

Studies in hypertensive individuals, in diabetic patient, and also in general populations showed that the nighttime SBP more accurately predicted future cardiovascular events than the daytime SBP, especially in hypertensive treated patients.<sup>21</sup> Impaired circadian modulation of sympathovagal activity is probably involved in the reduced nocturnal BP fall observed in diabetic patients.<sup>12,22</sup>

In the group of reverse dippers, circadian acrophase of BP (i.e. the time of the maximum of the BP) in diabetic patients occurring 1.5 hour earlier than in non-diabetics. Matteucci et al. showed that people with diabetes mellitus, both type 1 and 2, have their circadian acrophase (i.e. time of the maximum of the DBP) of diastolic blood pressure occurring 2–4 hours earlier than normotensive and hypertensive subjects.<sup>23</sup> Cardiovascular events tend to have higher incidences in the early morning hours, and morning BP or the early morning BP surge may contribute to this phenomenon.<sup>24</sup>

Some studies shown that the 24-hour BP variability is also an independent predictor of target organ damage.<sup>8,25</sup> We found lower BP variability in the group of reverse dippers, probably because of their continuous 24-hour high blood pressures.

Regarding WCH, we found higher but non significant prevalence in diabetic group. White coat effect has been

considered a low-risk factor for CV events; however, when coexistent with diabetes WCH increases risk.<sup>26</sup> Kramer et al. investigated the effect of WCH on the impact of microvessel disease and showed that the WCH in diabetes typ 2 was associated with two-fold higher risk of diabetic retinopathy and nephropathy.<sup>27</sup> Masked hypertension is more frequent in diabetes and seems to be associated with higher risk of target organ damage (LVIM).<sup>15</sup> Higher prevalence of masked hypertension in diabetics could be a sign of inadequate and difficult to treat hypertension in these pts. We couldn't analyze difference on MH in our patients because of too small sample.

In summary, BP determination by ABPM is capable of more adequately stratifying hypertensive patients, especially those with diabetes mellitus and other cardiovascu-

lar risk factors. Therefore, we believe that ABPM should be more used in our patients for better risk stratification and improving CV outcomes. Main limitations of this preliminary study are small sample size and its cross-sectional design, which precludes causal and temporal inferences. More findings on ABPM in our patients are expected after finishing HRKMAT Study and a continuous follow up.

### Acknowledgement

This study is part of nation-wide survey and register on ambulatory blood pressure monitoring (HRKMAT) which is organized, conducted and supported by the Croatian Society of Hypertension. This project is partly supported by Sanofi, Croatia.

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## KONTINUIRANO AMBULATORNO MJERENJE ARTERIJSKOG TLAKA KOD HIPERTONIČARA SA ŠEĆERNOM BOLESTI-PRELIMINARNI REZULTATI

### SAŽETAK

KMAT (kontinuirano ambulantno mjerenje arterijskog tlaka) je korisna metoda u dijagnostici i upravljanju arterijske hipertenzije i bolji predskazatelj budućih kardiovaskularnih događaja u usporedbi sa konvencionalnim ambulantnim mjerenjem AT (arterijskog tlaka). Unatoč potencijalnoj korisnosti KMAT još uvijek nije dovoljno zastupljen u svakodnevnoj kliničkoj praksi, uglavnom zbog pomanjkanja znanja te nedostupnosti aparata. Cilj ovog preliminarnog istraživanja jest odrediti kontrolu hipertenzije kao i karakteristični dnevni ritam AT kod pacijenata iz našeg centra koji su uključeni u »HRKMAT« Studiju – Hrvatski registar kontinuiranih mjerača tlaka. Iako pacijenti uključeni u ovu studiju imaju višestruke faktore rizika za kardiovaskularne bolesti, u ovom članku smo analizirali razlike između hipertenzivnih dijabetičara (N=20) i nedijabetičara (N=57). KMAT je učinjeno sa automatiziranim oscilometrijskim uređajem Mobil-O-Graph NG Vers.20. Prosječni ambulantni krvni tlak je bio 139/90 mmHg, a srednji 24-satni krvni tlak 130/82 mmHg. Većina hipertenzivnih bolesnika je uzimala antihipertenzivne lijekove (79,2%). Dijabetičari su imali viši sistolički, ali niži dijastolički tlak. Nije bilo statistički značajne razlike u »dipping« statusu, ali zamijećen je raniji jutarnji porast AT kod dijabetičara sa noćnim porastom tlaka u odnosu na nedijabetičare s noćnim porastom tlaka. Iako nismo našli statistički značajnu razliku »hipertenzija bijelog ogrtača« je bila češća kod dijabetičara, a samo dvoje pacijenta je imalo maskirnu hipertenziju. Ovo su preliminarni rezultati KMAT-a iz našeg centra i HRKMAT registra. Više vrijednjih podataka i rezultata se očekuje iz glavne HRKMAT baze podataka.