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Ph.D. THESIS

**THE IMPORTANCE OF BLOOD PRESSURE
AMBULATORY MONITORING PROFILE OF THE
ELDERLY CORRELATED WITH ORGAN DAMAGE**

A B S T R A C T

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Keywords: Blood pressure in elderly, ABPM, Masked hypertension, White coat hypertension, cardiac organ damage, renal organ damage

1. INTRODUCTION - MOTIVATION

Hypertension is a disease widespread worldwide and it's also affecting the majority of the population of this country. The consequences of this disease are multiple and severe, most important of them are the decrease in the quality of life of the patients with the increase of the mortality rate due to cardiovascular diseases.

Medical guidelines indicate ABPM (Ambulatory Blood Pressure Monitoring based on the use of 24hour BP holter) as the gold standard technique used in the detection of the patient's BP profile.

This Ph.D. thesis subject brings in front the relationship between the importance of early and correct detection of the BP profile of elderly treated hypertensive patients, and the presence of target organ damage, which can be used to improve the management of hypertension patient's cases in the general practitioner office and to emphasize the need of using this technique by them in the secondary prevention of the BP different profiles.

2. GENERAL PART

Hypertension is a chronic disease that has a high prevalence, among elderly people. Confirming the diagnose as early as possible and establishing the appropriate treatment helps taking under control the long-term effects and preventing the occurrence of the organ damage.

After performing ABPM on uncontrolled hypertension in elderly treated hypertensive patients were identified the following BP profiles:

- ❖ **CH** = Controlled Hypertension→ Clinic BP<140/90mmHg; Ambulatory BP <130/80mmHg;
- ❖ **WCEUH** = White Coat Effect on Uncontrolled Hypertension→ Clinic BP≥140/90mmHg; Ambulatory BP<135/85mmHg;
- ❖ **MEUH** = Masked Effect on Uncontrolled Hypertension→ Clinic BP <140/90mmHg; Ambulatory BP>130-135/85mmHg;
- ❖ **SUH** = Sustained Hypertension→ Clinic BP≥140/90 mmHg; Ambulatory BP≥130/80mmHg.

In many clinical studies, it has been observed that WCEUH and MEUH correlate with organ damage, even more MEUH BP profile, which causes an increase in fatal cardiovascular and cerebral events, with inference on patients' quality of life.

In medical publishing database, there is evidence for the correlation between nondipper pattern category in hypertensive elderly patients and cardiac and renal organ damage.

ABPM use in current practice demonstrated that by determining as early and accurately as possible the patient's BP profiles, a strong impact on target organ damage will be registered. Several studies agreed that in hypertensive patients target organ damage, meaning the presence of left ventricular hypertrophy, increased carotid intima-media thickness, increased urinary albumin/urinary creatinine ratio, and others, correlates rather with ambulatory blood pressure monitoring than with clinical blood pressure monitoring. Organ damage has a huge impact on patient quality of life by increasing the mortality and morbidity rate, which automatically is not something we would want to happen.

In the future, in daily practice in the general practitioner's office, ABPM can be used for secondary prevention of BP profiles as WCEUH and MEUH in elderly treated hypertensive patients with uncontrolled hypertension, and also for secondary prevention of dipper patterns due to the implications that these profiles have on target organ damage, meaning they are predictors of cardiac and renal damage, and also because of the incidence of fatal cardiovascular events which increases the mortality rate.

Other researchers managed to show that masked hypertension profile is more correlated with either cardiac and renal organ damage than white coat hypertension profile, which means that ABPM is even more useful in the detection and monitoring of BP profiles especially in masked BP profile due to the specificity of the measurements and furthermore to the administration of the appropriate treatment according to those measurement values which will reduce the rate of fatal cardiovascular events and increase the quality of life of the patients.

Identifying BP profiles, BP dipper patterns and the values of different parameters by using ABPM sums up the prediction of cardiac damage which helps to choose the optimal management in each case.

In a study conducted on a group of 2974 hypertensive patients was shown that after using ABPM, the blood pressure profiles obtained were correlated with

renal damage identified by increased values of the urinary albumin/ urinary creatinine ratio stronger in masked and white coat BP profiles compared to normotension BP profile. The final conclusion of this study was that due to these correlations MUCH and WCEUH profiles require faster detection and specific monitorization.

So ABPM should be used in the secondary prevention of masked uncontrolled hypertension pattern in treated hypertensive patients, in general practitioner's office, by identifying the BP profile and the dipper BP pattern, because of the implications of this BP profile as a predictor for cardiac and renal organ damage, and also because of the fatal cardiovascular events with an increase in the mortality rate.

3. SPECIFIC PART

3.1. SCOPE AND OBJECTIVES

This research thesis aims to establish through a cross-sectional observational study the importance of using ABPM in the detection of BP profile in elderly treated hypertensive patients to emphasize the utility of ABPM in the general practitioner office, especially for the early determination of BP profiles and because of their implications in the development of organ damage

The objectives of this thesis are:

1. Establishing BP profile patterns of elderly known hypertensive patients with uncontrolled hypertension treated for at least one year with antihypertensive drugs, by using ABPM and also the prevalence of masked hypertension effect and white coat effect on uncontrolled hypertension in this group of patients.
2. Establishing the impact of BP profiles on cardiac and renal organ damage, in our case.
3. Establishing the correlation of ABPM parameters with organ damage and demonstrating it's implication on patient's quality of life.
4. Demonstrating the importance of using ABPM in the secondary prevention of the effect of masked hypertension in the general practitioner office.

3.2. MATERIAL AND METHODS

This cross-sectional study was conducted on a period of two years (January 2017 – December 2018), with the participation of elderly hypertensive patients from three general practitioner offices in Timiș county, who were treated with antihypertensive medication for at least one year. The research plan was approved by the Ethics committee of "Victor Babeș" University of Medicine, Timisoara. Patients signed an informed consent document.

BP profile was established after the measurement of clinic and ambulatory BP. Clinic BP was determined as the mean value of three repeated BP measurements in general practitioner office and ambulatory BP was determined as the mean value of 24 hours BP measurements after using ABPM. Cardiac organ damage was established by the presence of left ventricular hypertrophy on the electrocardiogram, and renal damage was established by the high value of urinary albumin/urinary creatinine ratio calculated after biological investigations were done. Other parameters like daytime 24h BP, nighttime 24h BP, 24h pulse pressure and nocturnal dipping categories were also determined. Once the database was completed, SPSS version 20 was used and statistical tests were performed in order to identify the relationships between the BP profile category or other parameters and the presence of target organ damage.

3.3. RESULTS

3.3.1. Descriptive statistics

In the study group were included 437 patients after performing the inclusion and exclusion criteria with the following characteristics of the group: median age 74.06 ± 5.81 years, 57% of them were young-old patients, 37.8% were middle-old patients, 5.3% were oldest-old patients; 58.8% female, and 72.1% from the urban area.

The characteristics of the study group are the following: young-old patients group is the biggest, more than the majority of them are male and are coming from the rural area; middle-old patients group is the second biggest group, more than the majority of them are female and are coming from the rural area; oldest-old patients group is the smallest group, the majority of them are male and are coming from the urban area.

3.3.2. Determination of study group significant characteristics in terms of bp profiles and their relation with clinical data, anthropometric measurements, and biochemical investigations

The distribution of BP profiles in the sample was: CH>MEUH> SUH> WCEUH.

We identified the following data for each of the BP profiles: Characteristics of the CH subgroup: 178 patients (40.73% of the total), young-old, obese, 62.9% female, 74.7% from the urban area, 25.8% smokers, 12.9% moderate alcohol consumer, with total cholesterol, LDL cholesterol, and serum triglyceride values slightly increased, HDL cholesterol, serum creatinine, and ACR normal limits;

Characteristics of the WCEUH subgroup: 63 patients (14.41% of the total), young-old, obese, 50.8% male, 68.3% from the urban area, 9.5% smokers, 9.5% moderate alcohol consumption, with total cholesterol, LDL cholesterol, and serum triglyceride values slightly increased, HDL cholesterol, serum creatinine, and ACR normal limits;

Characteristics of the MEUH subgroup: 89 patients (20.36% of the total), young-old, overweight, 53.9% female, 73.0% from the urban area, 24.7% smokers, 27% moderate alcohol consumer, with total cholesterol, LDL cholesterol, and triglyceride values slightly increased, HDL cholesterol, serum creatinine, and ACR normal limits;

Characteristics of the SUH subgroup: 107 patients (24.48% of the total), young-old, overweight, 58.8% female, 72.1% from the urban area, 22% smokers, 14.2% moderate alcohol consumer, with total cholesterol, LDL cholesterol, and triglyceride values slightly increased, HDL cholesterol normal limits, serum creatinine slightly increased and ACR normal limits.

We used Z test with Bonferroni correction and found p value significant for ACR ($p=0.001$), total cholesterol ($p=0.001$) for all BP profiles, ex-smoker status ($p=0.026$) in CH, WCEUH, SUH, non-smoker status ($p=0.026$) in MEUH, non-alcoholic status ($p=0.009$) in WCEUH, MEUH, SUH, occasional alcohol consumer ($p=0.009$) in CH.

3.3.2. Determination of study group significant characteristics in terms of bp profiles and their relation with parameters values and dipper patterns

Characteristics of BP profiles obtained after Clinic BP and ABPM measurements and the distribution of dipper pattern for nocturnal systolic and diastolic BP:

CH BP profile → patients with clinical BP values in normal limits, ABPM BP values in normal limits, nondipper status (Nocturnal SBP: nondipper> dipper> reverse dipper> extreme dipper, Nocturnal DBP: nondipper> dipper> reverse dipper> extreme dipper); **WCEUH BP profile** → patients with raised clinical BP values, ABPM BP values in normal limits, nondipper status (Nocturnal SBP: nondipper> dipper> reverse dipper> extreme dipper, Nocturnal DBP: nondipper> dipper> reverse dipper> extreme dipper); **MEUH BP profile** → patients with clinical BP values in normal limits, ABPM BP values raised, nondipper status (Nocturnal SBP: nondipper> dipper> reverse dipper> extreme dipper, Nocturnal DBP: nondipper> dipper> reverse dipper> extreme dipper); **SUH BP profile** → patients with raised clinical BP values, ABPM BP values raised, dipper status (Nocturnal SBP: dipper> nondipper> extreme dipper> reverse dipper, Nocturnal DBP: nondipper> dipper> extreme dipper> reverse dipper);

After performing ANOVA in all BP profiles (CH, WCEUH, MEUH, SUH) a p value <0,001 was found for the following parameters: Clinic_SBP, Clinic_DBP, Clinic_PP, ABPM_SBP_24h, ABPM_DBP_24h, ABPM_PP_24h, ABPM_SBP_daytime, ABPM_DBP_daytime, ABPM_PP_daytime, ABPM_SBP_nighttime, ABPM_DBP_nighttime, ABPM_PP_nighttime, SBP_dipping, SBP_dipping.

3.3.4. Determination of organ damage predictors

3.3.4.a. Determination of cardiac organ damage predictors

The presence of cardiac damage within BP profiles in the studied sample was identified as following: 39.9% in the CH group, 38.1% in the WCEUH group, 42.7% in the MEUH group, 63.6% in the SUH group.

For cardiac damage after using logistic regression → the negative predictors for LVH were: PP p=0.001 (ABPM_PP_daytime (1.116 (95%CI 1.053-1.184)) better predictor than ABPM_PP_24h (1.103 (95%CI 1.063-1.145)) and than ABPM_PP_nighttime (1.06 (95%CI 1.025-1.097))) and DBP_dipping_nondipper (1.654 (95%CI 1.225-2.234)) p=0.001;

→ the positive predictors for LVH were: ABPM_SBP_24h (0.957 (95%CI 0.917-0.999)) p=0.044 and ABPM_DBP_daytime (0.947 (95%CI 0.907-0.989)) p=0.013.

3.3.4.a. Determination of renal organ damage predictors

The presence of renal damage within BP profiles in the studied sample was identified as following: 39.3% in the CH group, 36.5% in the WCEUH group, 44.9% in the MEUH group, 60.7% in the SUH group.

For renal damage after using logistic regression → the positive predictors for were: ABPM_SBP_daytime (0,977 (95%CI 0,965-0,989)) p=0.001, and ABPM_DBP_nighttime (0,964 (95%CI 0,942-0,986)) p=0.002.

3.4. DISCUSSION

In the study patient profile has the following characteristics: young-old category (57% of the total, mean age 74.06 ± 5.81 years), female (58.8%), overweight (32.5%), living in the urban area (72.1%), ex-smoker status (40.5%), non-alcoholic consumption (43.2%), BP profile CH, with high values of total cholesterol, LDL cholesterol and serum triglycerides and HDL cholesterol values within normal limits. These characteristics of the study cohort are in many ways similar to the characteristics of the patients included in the SEPHAR study conducted in Romania including female sex, urban area, smoker status (ex-smoker status), increased values of lipid profile, and except HDL cholesterol.

We can still observe that the study subgroups are approximately homogeneous if we look at the characteristics described, even though they have different numbers of participants. In all four cases a significant p-value can be observed for ACR and total cholesterol values which is a warning for the possible development of organ damage.

One of the objectives of this study was to determine and characterize BP profiles of the patients included in the study:

MEUH BP profile – prevalence 20,36%, for all clinic or ABPM BP measurements and obtained parameters p <0,001;

WCEUH BP profile – prevalence 14,41%, for all clinic or ambulatory BP measurements and obtained parameters p<0,001;

SUH BP profile – prevalence 24%, for all clinic or ambulatory BP measurements and obtained parameters p<0,001.

CH BP profile – prevalence 40,73%, for all clinic or ambulatory BP measurements and obtained parameters $p < 0,001$.

Cardiac damage within the group sample shows a stronger correlation with SUH and MEUH BP profiles than with the other two BP profiles. Also, this correlation was identified by Jan Filipovsky, in his study, who later recommended for patients with these BP profiles repeated measurements of the blood pressure and optimal treatment in the management of the case.

In the study, we tried to identify which of the ABPM parameters are independent predictors for cardiac damage. We were able to identify PP and DBP dipping nondipper as negative predictors for cardiac damage: ABPM_PP_daytime is the strongest predictor for LVH $p < 0.001$ OR 1.116 (95% CI 1.053-1.184) followed by ABPM_PP_24h $p < 0.001$ OR 1.103 (95% CI 1.063-1.145), and then by ABPM_PP_nighttime $p < 0.001$ OR 1.06 (95% CI 1.025-1.097). DBP_dipping_nondipper is an important predictor $p = 0.001$ OR 1.654 (95% CI 1.225-2.234). The positive predictors parameters were: ABPM_24h_SBP $p = 0.044$ OR 0.957 (95% CI 0.917-0.999) and ABPM_daytime_DBP $p = 0.013$ OR 0.947 (95% CI 0.907-0.989)). Another study conducted on a group of elderly hypertensive patients also showed that the parameters obtained by ABPM measurements, like Pulse Pressure and daytime SBP, were correlated with cardiac damage, so it was concluded that ABPM should be used in finding the correlations between BP different parameters and organ damage. In Olesen et al. study pulse pressure is also considered a predictor of cardiac damage: ABPM_PP_24h is a predictor of the cardiac damage for the elderly group from the study $p = 0.001$ (OR 1.24, 95% CI 1.09-1.42). Araujo et al. demonstrated the association between nondipper pattern and cardiac organ damage, especially in older hypertensive patients. Hermida et al. also suggested the association between nondipper pattern and an increased risk of developing cardiovascular events, and also the usefulness of ABPM in establishing this relationship. Another idea of the study described above is directed on the importance of using ABPM for the detection and control of BP parameters in stage of clinic or home BP measurements, because of the BP parameters that were found out to be predictors of LVH detected by ECG. We also support the idea of using ABPM in detecting both the BP profiles and the predictive parameters of cardiac damage in general practitioner office.

Renal damage within the group sample shows a stronger correlation with SUH and MEUH BP profiles than with the other BP profiles. Drawz et al. also

identifies a correlation between masked hypertension BP profile and organ damage, and indicates ABPM as the most appropriate method in detecting BP profiles for the hypertensive patients with renal organ damage.

The predictors of renal damage were ABPM_nighttime_DBP $p=0.002$ OR 0.964 (95% CI 0.942-0.986), and ABPM _daytime_SBP $p=0.001$ OR 0.977 (95% CI 0.965-0.989) as positive predictors, so we can say that our findings are similar with those mentioned in the study of Olesen et al. which managed to show that renal damage expressed by ACR was 0.26 (0.10-0.52) mg/mmol for the elderly group couldn't identify a negative predictor for ACR in the BP parameters measured by ABPM. According to Drawz et al., renal damage is associated with different parameters obtained by ABPM measurements (95% CI 0.7-1.1) in masked hypertension BP profile, which is also a new reason for using ABPM in the secondary prevention of masked uncontrolled hypertension BP profile in the primary care.

We can say that in the present research paper we managed to identify the predictive factors of cardiac and renal organ damage in elderly hypertensive patients with uncontrolled BP values as others managed to show in their studies.

4. CONCLUSIONS

Study objectives were reached, the results obtained were positives ones, but especially in agreement with those from medical research databases.

The first objective of the study: once we established BP profiles of the patients we observed that MEUH prevalence was higher than WCEUH prevalence but lower than SUH and CH prevalence.

The second objective of the study: we noticed that all BP patterns significantly correlated with LVH presence (SUH and MEUH more than CH and WCEUH), but also with increased values of urinary albumin/creatinine ratio (SUH), concluding that MEUH is the most important BP profile which has to be identified as sooner as possible to stop the evolution of cardiac organ damage and that sustained BP values can increase renal damage.

The third objective of the study: regarding cardiac damage we identified many predictors such as ABPM_PP_daytime, ABPM_PP_24h, ABPM_PP_nighttime, and DBP_dipping_nondipper which are negative predictors, but also ABPM_SBP_24h

and ABPM_DBP_daytime as positive predictors; regarding renal damage we identified ABPM_DBP_nighttime and ABPM_SBP_daytime as positive. Because we identified that the parameters obtained by performing ABPM are predictors for organ damage we can conclude that ABPM is necessary in the case management of elderly treated hypertensive patients.

The fourth objective of the study: the prevalence of MEUH hypertension profile in the sample is quite high compared to the prevalence of WCEUH hypertension profile; almost half of the subjects in the MEUH subplot have heart and renal organ damage; cardiac and renal organ damage predictors were identified among the parameters of blood pressure profiles obtained after ABPM. These results demonstrate the importance of using ABPM for the secondary prevention of masked uncontrolled hypertension profile in elderly treated hypertensive patients, in the general practitioner's office.