ARTICLE ORIGINAL

Prognostic value of ambulatory blood pressure monitoring in treated hypertensive patients

Valeur pronostique de la mesure ambulatoire de la pression artérielle chez les patients hypertendus traités

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Abstract

Introduction : Ambulatory blood pressure monitoring (AMBP) has become a valuable tool for analyzing patient blood pressure (BP) profile to make a more accurate prognosis compared to clinical office BP.

Aim: To identify the prognostic value of different parameters of ABPM and the future course of cardiovascular events (CVE) in treated hypertensive patients.

Methods : We conducted a prospective, descriptive study, including treated hypertensive patients which had consulted between 2015 and 2016 and had a systematic ABPM during their follow-up. Patients were followed at the outpatient clinics for 4 years, and we searched in the computerized medical file the occurrence of CVE.

Results : A total of 240 patients were included in our study with masculine predominance (57%). The mean age was 57.4±9.5 years. During 4 years of follow-up, 30 patients (12.5%) experienced a CVE. The total number of CVE was 32: acute heart failure (3), acute coronary syndrome (15), atrial fibrillation (12), stroke (2). Daytime systolic blood pressure (SBP), night-time SBP, 24-h SBP and 24-h pulse pressure (PP), had similar performances to predict CVE. Only the 24-h PP (OR= 1.072; 95% IC: 1.019-1.128; p= 0.007) was found to be an independent predictor of CVE. A 24-h PP> 55 mmHg increased the risk of CVE by 3.2.

Conclusion : SBP and PP were associated with CVE in treated hypertensive patients. the 24-h PP was found to be an independent predictor of CVE so it may serve as a therapeutic target in hypertension therapy.

Key words : Ambulatory blood pressure monitoring, hypertension, prognosis

Résumé

Introduction : La mesure ambulatoire de la pression artérielle (MAPA) est devenue un outil précieux pour analyser le profil de la pression artérielle (PA) du patient afin d'établir un pronostic plus précis par rapport à la PA mesurée au cabinet médical.

Objectif : Déterminer la valeur pronostique des différents paramètres de la MAPA et la survenue des événements cardiovasculaires (ECV) chez les patients hypertendus traités.

Méthodes : Nous avons mené une étude prospective et descriptive, incluant les patients hypertendus traités ayant consulté entre 2015 et 2016 et ayant eu une MAPA au cours de leur suivi. Les patients ont été suivis en ambulatoire pendant 4 ans, et nous avons recherché dans le dossier médical informatisé la survenue des ECV

Résultats : Au total, 240 patients ont été inclus dans notre étude avec une prédominance masculine (57%). L'âge moyen était de 57,4±9,5 ans. Au cours des 4 années de suivi, 30 patients (12,5 %) ont présenté un événement cardiovasculaire. Le nombre total de ECV était de 32 : insuffisance cardiaque aiguë (3), syndrome coronarien aigu (15), fibrillation auriculaire (12), accident vasculaire cérébral (2). La pression artérielle systolique diurne (PAS-diurne), la pression artérielle systolique nocturne (PAS-nocturne), la pression artérielle systolique sur 24 heures (PAS-24 h) et la pression pulsée sur 24 heures (PP-24 h) avaient des performances similaires pour prédire les ECV. Seule la PP-24 h (OR= 1.072 ; 95% IC : 1.019-1.128 ; p= 0.007) s'est avérée être un facteur prédictif indépendant de l'ECV. Une PP-24 heures > 55 mmHg augmentait le risque de ECV de 3,2.

Conclusion : La PP-24 h s'est avérée être un facteur prédictif indépendant de l'ECV et pourrait donc devenir une cible thérapeutique dans le traitement de l'hypertension artérielle.

Mots clés : mesure ambulatoire de la pression artérielle, hypertension artérielle, pronostic

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INTRODUCTION

Arterial hypertension is the first chronic disease in the world. This pathology causes a considerable morbidity and mortality [1].
Office blood pressure (BP) measurement has been the basis for both establishing the relationship between BP and prognosis and for treatment decisions focused on cardiovascular protection [2,3]. However, over the past three decades, ambulatory blood pressure monitoring (AMBP) has become a valuable tool for analyzing patient blood pressure profile to make a more accurate prognosis compared to clinical BP [4–8].

ABPM has become important since it ensures the diagnosis of certain specific forms, such us masked and white coat hypertension. Also, it is the only tool for the diagnosis of isolated nocturnal hypertension. Additionally, several AMBP-derived parameters have been reported as important predictors of cardiovascular risk, as had been addressed in several trials [4,8–12]. However, most of the studies determining the predictive value of ABPM have been carried out in the general population or in cohorts of hypertensive patients, before the initiation of treatment. Studies in patients who have already been treated are relatively rare, and they have generally focused on resistant hypertension or on the comparison between ABPM and self-measurement of BP [13,14].

Thus, we aimed to identify the prognostic value of different parameters of ABPM and the future course of cardiovascular events (CVE) in treated hypertensive patients.

METHODS

Study design

We conducted a prospective, longitudinal, descriptive study, including treated hypertensive patients which had consulted between 2015 and 2016 and had a systematic ABPM during their follow-up. Data collection was done at the outpatient clinic of cardiology department of the internal security forces hospital of Marsa.
The inclusion criteria were the following: (a) patients aged more than 18 years old (b) with sinus rhythm on the electrocardiogram and (c) diagnosed and treated for hypertension.
The patients with invalidated ABPM were excluded.
All patients eligible for the study had a clinical examination with measurement of blood pressure in the office, before wearing the device, and a biological examination with a search for target organ damage.

Ambulatory Blood Pressure Measurements

ABPM was performed with devices of the Spacelabs type, validated according to the recommendations of the European Society of Hypertension, on a regular working day, during the normal intake of the usual antihypertensive treatment. Following the standard protocol, recording began between 8:30 and 9 AM, with readings every 15 minutes during the day and every 30 minutes during the night. The patients were instructed to maintain their usual activities, return the following morning for device removal, and keep the arm extended and immobile at the time of each cuff inflation. Before starting the study, reliability of BP values measured with the monitor were checked against simultaneous measurements with a mercury sphygmomanometer. Differences of < 5 mm Hg were allowed. AMBP is considered reliable and correctly interpretable if at least 70% of measurements were valid with at least 20 diurnal, 7 nocturnal and no more than two consecutive hours without measurement.

Follow-up of the patients

After the initial evaluation, patients were followed at the outpatient clinics for 4 years, and we searched in the computerized medical file the occurrence of the following CVE: acute heart failure (AHF), acute coronary syndrome (ACS), Atrial fibrillation (AF) onset, stroke and death. The sum of these events was the combined endpoint. Antihypertensive treatment was monitored by means of frequent office BP measurements, and when appropriate changes in the number, class, and dose of antihypertensive drugs (diuretics, b-blockers, a-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors and vasodilators) were made according to clinical criteria (goal of BP control <140/90 mm Hg) in spite of whether treating physicians were or were not aware of the ABPM results.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics 23 software. The Kolmogorov-Smirnov test was used to evaluate whether the distribution of continuous variables was normal.
Values were expressed as mean ±SD or median with percentiles. Qualitative variables were expressed as single or relative frequencies.
Differences between groups were sought by using Student's t test for continuous variables and chi-square test for discontinuous variables.
The determination of the cut-off values of the studied parameters was made by analyzing their receiver operating characteristic (ROC) curves with comparison of the areas under the curve by the Delong method. Binary logistic regression analysis was performed for the multivariate study. In all statistical tests, the significance level was set at 0.05.

RESULTS

General Characteristics

A total of 240 patients were included in the present study. They were 137 (57%) men and 103 (43%) women, with a mean age of 57.4±9.5 years. Mean body mass index (BMI) was 29.2 ± 4.9 kg/m². Twenty-three percent were current smokers, 42% had type 2 diabetes and 32% had dyslipidemia. Nearly 30% of the population had at least three cardiovascular risk factors associated with hypertension. A history of previous cardiovascular disease was present in 24%. The most prescribed antihypertensive treatment was renin-angiotensin antagonists, followed by calcium channel blockers, diuretics then beta-blockers.

Forty-three percent of patients were on monotherapy, 35% on dual therapy, 18% on triple therapy and 4% on quadruple therapy.

The mean duration of hypertension was 7.5 years, mean office BP was 144.2 ±21.8 /79.6 ±11.1 mmHg and mean 24-h BP was 129.5 ±14/74.7 ±9.8 mmHg. Sixty-eight percent of the population had grade 1 hypertension.

During 4 years of follow-up, 30 patients (12.5%) experienced a cardiovascular event. The total number of events was 32: AHF (3), ACS (15), AF onset (12), stroke (2). No patients died and 24 were lost to follow-up after an average period of 10 months. The mean time to onset of CVE was 14.5 ± 9 months.

Analytic study

Table 1 shows baseline characteristics between patients who suffered or not a CVE. In comparison with those who remained free from events, those who experienced an event were significantly older, more likely to be diabetics and showed more frequently an history of a previous cardiovascular disease. After ABPM analysis, the group of patients with CVE had significantly higher 24-h SBP, 24-h PP, daytime SBP and night-time SBP. These patients were significantly more reverse dipper with lower diastolic dipping. Fasting glucose and glycated hemoglobin were significantly higher in patients with cardiovascular event.

Table 1. baseline characteristics between patients who suffered or not a cardiovascular event

		General population	Patients with CVE	Patients without CVE	P
Age (years)		57.4 ± 9.5	62.1 ± 12	56.7 ± 8.9	0.023
Sex Male (%)/Female (%)		103 (43)/137 (57)	10 (33)/20 (67)	117 (56)/93 (44)	0.325
Diabetes (%)		101 (42)	18 (60)	83 (40)	0.047
Smokers (%)		55 (23)	7 (23)	48 (23)	0.984
Dyslipidemia (%)		76 (32)	10 (33)	66 (31)	0.836
history of previous cardiovascular disease (%)		58 (24)	12 (40)	46 (22)	0.040
Number of CVRF		3 [2-4]	3 [2-4.25]	3 [2-4]	0.077
BMI (kg/m2)		29.2 ± 4.9	28.7 ± 5.6	29.2 ± 4.8	0.817
Office SBP (mmHg)		140 [130-160]	144.5 [130-157]	140 [130-160]	0.564
Office DBP (mmHg)		80 [70-80]	80 [70-87.7]	80 [70-80]	0.926
Heart rate (pulse/min)		72 ±11	79 ± 12	72 ±11	0.630
24-h SBP (mmHg)		128 [119-138]	132.5 [124-147]	127 [118-137]	0.011
24-h DBP (mmHg)		73 [68-80]	73 [68.5-79]	74 [68-80]	0.762
24-h PP (mmHg)		53 [47-60]	58.5 [53-68]	52 [47-59]	0.002
Daytime SBP (mmHg)		131 [121-141]	135 [125-150]	130.5 [121-141]	0.016
Daytime DBP (mmHg)		76 [70-83]	74.5 [69-80]	76.5 [70-83]	0.397
Night-time SBP (mmHg)		120 [112-133]	128.5 [113-144]	119 [111-131]	0.010
Night-time DBP (mmHg)		68 [62-74]	68 [60-75.25]	68 [62-74]	0.569
Systolic dipping (mmHg)		7 ± 7.3	4.6 ± 8.4	7.3 ± 7.1	0.057
Diastolic dipping (mmHg)		10.8 ± 8.2	7.5 ± 10	11.3 ± 7.8	0.025
Dipping state (%)	Normal dipper	50 (21)	6 (20)	44 (21)	0.852
	Low dipper	150 (52)	13 (43)	112 (53)	0.334
	Extreme dipper	30 (13)	3 (10)	27 (13)	0.763
	Reverse dipper	34 (14)	8 (27)	26 (13)	0.036
Creatinine (µmol/l)		71 [59-88]	77 [61-97]	71 [59-86]	0.372
Urea (mmol/l)		5.7 [4.2-6.5]	5.6 [4.6-8.1]	5.2 [4.1-6.3]	0.073
Total cholesterol (g/l)		1.8 ± 0.5	1.6 ± 0.37	1.8 ± 0.5	0.134
Fasting glucose (g/l)		1.16 [1-1.44]	1.35 [1-2]	1.15 [1-1.41]	0.049
glycated hemoglobin (%)		6.4 [5.7-8.2]	7.8 [5.7-9.3]	6.3 [5.7-8.1]	0.026
Hemoglobin (d/dl)		13.7 ± 1.6	13.3 ± 1.6	13.7 ± 1.5	0.126

Abbreviations: BMI: Body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure

To further determine ABPM parameters predicting cardiovascular events, ROC curve analysis was performed. 24-h SBP, 24-h PP, daytime SBP and night-time SBP had similar performances to predict cardiovascular events (figure 1, Table 2). Their cut-off values were: 131 (sensibility= 63%, Sp= 62%), 55 (specificty= 70%, Sp= 60%), 133 (sensibility= 60%, specificity= 59%) and 126 mm Hg (sensibility= 62%, specificity= 67%), respectively.

The result of univariate analysis is showed in table 3. A 24-h SBP> 131, 24-h PP> 55, daytime SBP> 133 and night-time SBP> 126 mm Hg increased the risk of cardiovascular event by 2.9, 3.2, 2 and 3.3 respectively.

A binary logistic regression analysis was used to identify independent predictors of CVE, as shown in Tables 4. The variables included were the ABPM parameters significantly associated to CVE in the univariate analysis. Among these parameters, only the 24-h PP (OR= 1.072; 95% IC: 1.019-1.128; p= 0.007) was found to be an independent predictor of CVE. And according to this multivariate regression model, every additional point in the 24-h PP was independently associated with 7.2% increase in risk of CVE during long term follow-up.

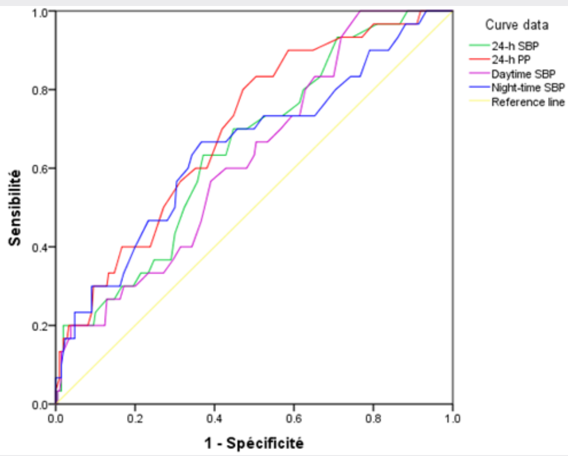

Figure 1. Receiver Operating Characteristic curve of ABPM parameters to predict cardiovascular event

Abbreviations: BMI: Body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure

Table 2. Area under Receiver Operating Characteristic curve of ABPM parameters to predict cardiovascular event with Delong test

	AUC	P value	95% CI	
			IB	SB
24-h SBP	0.651	0.008	0.551	0.750
24-h PP	0.699	<0.001	0.605	0.793
Daytime SBP	0.626	0.025	0.528	0.725
Night-time SBP	0.652	0.007	0.540	0.763

	AUC differences	P value (Delong)
24h-PP Vs Daytime SBP	0.073	0.074
24h-PP Vs 24-h SBP	0.048	0.188
24h-PP Vs Night-time SBP	0.047	0.306
Night-time SBP Vs Daytime SBP	0.025	0.539
24-h SBP Vs Daytime SBP	0.024	0.107
Night-time SBP Vs 24-h SBP	0.001	0.969

Abbreviations: BMI: Body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; AUC: area under curve

Table 3. Univariate analysis of ABPM parameters to predict cardiovascular events

	Cut-off	Sensibility	Specificity	Odds ratio	%95 IC		P
					IB	SB	
24-h SBP	131	63%	62%	2.9	1.32	6.46	0.009
24-h PP	55	70%	60%	3.2	1.41	7.40	0.005
Daytime SBP	133	60%	59%	2	0.91	4.36	0.151
Night-time SBP	126	62%	67%	3.3	1.49	7.33	0.004

Abbreviations: BMI: Body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure

Table 4. Area Multivariate analysis of ABPM parameters to predict events

	P	Odds Ratio	95% CI	
			IB	SB
24-h SBP	0.290	0.917	0.780	1.077
24-h PP	0.007	1.072	1.019	1.128
Daytime SBP	0.281	1.077	0.941	1.231
Night-time SBP	0.846	1.009	0.918	1.109
Diastolic dipping	0.373	0.960	0.876	1.051
Reverse dipper	0.279	0.439	0.099	1.951

Abbreviations: BMI: Body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure

DISCUSSION

The present study, conducted in selected hypertensive patients followed at our outpatient clinics, shows that ABPM is correlated to prognosis and among its different parameters, 24-h PP is the most powerful prognostic factor of cardiovascular events.

Published reports on ABPM and prognosis on hypertensive subjects in the literature share some results of our study. Lempiäinen and al. aimed to evaluate ambulatory PP as a long-term risk factor in a random cohort of 900 middle-aged participants who attended the OPERA study [15]. The authors found that high nighttime ambulatory PP predicted independently CV mortality (HR= 2.60; 95%CI : 1.08–6.31, p=.034) and all-cause mortality (HR= 1.72; CI 95% 1.06–2.78, p=.028).

In a similar study, authors aimed to investigate the predictive value of pulse pressure on cardiovascular events in 2045 participants from the PAMELA study. They found that 24-h PP were independent predictors of CVE and total mortality during follow up (HR= 1.919; CI 95% 1.733–2.212, p< 0.001) [16].

The increasing of PP is a phenomenon usually seen with aging as SBP rises with age, while DBP begins to gradually decline after a plateau phase between 50 and 60 years [17]. The widening of PP is mostly due to reduced arterial elasticity, and PP is often considered as a surrogate measure for arterial stiffness.

In view of this idea, Khattar and al. found that 24-h, daytime and night-time PP were recognized as better prognostic factors for CV events in a group of 60 years of age or older, compared with a younger group [18].

In a comparative outcome trial with previously untreated elderly hypertensive patients, nighttime ambulatory PP was the most consistent pretreatment BP predictor of all-cause and CV mortality follow-up [19].

Staessen and coworkers reported that high nighttime PP increased the risk of all cause and CV mortality in hypertensive patients over 60 years of age attending the placebo group [20].

In a Tunisian study, the authors showed that nocturnal blood pressure was most often poorly controlled and responsible for microangiopathy [21].

The reason why PP is an independent predictor for CVE remains unknown. Several morbidities may potentially increase PP and CVE. In our study, both diabetes and history of previous cardiovascular disease were significantly associated with CVE as well as aging. In fact, arterial stiffness increases SBP which is responsible for widening of PP.

In the present study, a 24-h PP> 55 (OR= 3.2, Se= 70%, Sp= 60%) was the optimal cut-off to predict CVE during follow up.

Using data from 1257 participants without a history of cardiovascular disease and followed for 4.84 years, Zhang and al. recently found that the optimal cutoff points of a wide PP for predicting the risks of cardiovascular events and all-cause death were 70.25 and 76.25 mmHg, respectively [22].

Many other published reports showed that a PP value of >50 [23], >60 [1], >70 [24] or >80 mmHg [25] is associated with cardiovascular risk and organ damage.

Differences in cutoffs defining a wide PP among these studies may be due to differences in population characteristics and ethnic backgrounds.

In the present study, the other ABPM parameters predicting cardiovascular events alongside with 24-h PP were 24-h SBP, daytime SBP and night-time SBP.

Previous trials prioritized SBP over DBP as a predictor of cardiovascular events [26,27]. Moreover, additional studies reported that DBP was not independently associated with cardiovascular events [28], cardiovascular mortality [29], symptomatic peripheral artery disease [30], and target organ damage [31] in individuals regardless of age.

Current cardiovascular risk estimation tools [32] and hypertension guidelines [33] assign more importance to SBP and less to DBP. More recently, the Systolic Blood Pressure Intervention Trial [34] further promoted the benefits of intensive SBP control in high-risk cardiovascular patients and the benefit of the intensive SBP lowering did not differ by baseline DBP.

But contrary to our results, the Framingham Heart Study [35] demonstrated in a cohort of 6539 participants aged between 20 and 79 years, that DBP was the strongest predictor of coronary heart disease risk (HR per 10 mmHg increment: 1.34, 95% CI: 1.18–1.51) rather than SBP (HR: 1.14, 95% CI: 1.06–1.24) in the group <50 years of age.

Recently, hypertension guidelines [1] have focused more on SBP and DBP than PP control. Considering that studies identified PP as a risk factor for cardiovascular events and death, PP management may serve as a therapeutic target in hypertension patients. Williams and al. concluded that dietary supplementation with folic acid reduced PP and increased systemic arterial compliance independently of homocysteine or folate concentrations [36].

Some limitations have to be addressed to the present study. At first, our analysis was of a single-center design, and uses observational non-randomized data, thus it is subject to selection bias. Secondly, our study population was relatively small as compared with a number of large-scale studies found in literature. Besides, follow-up time was no longer compared to other studies. Furthermore, our database lacked data on drug regimen changes and patient's compliance after discharge, which have a significant impact on prognosis. Finally, it is possible that the present study is somewhat underpowered to accurately estimate the association between AMBP parameters and mortality. Further studies with a larger population and longer follow-up are needed to confirm our findings.

CONCLUSION

In conclusion, this prospective cohort study shows that SBP and PP are associated with cardiovascular events in treated hypertensive patients. The 24-h PP was found to be an independent predictor of CVE. The results indicate that shifts in both daytime and night-time SBP should be considered as cardiovascular risk factors, and PP may serve as a therapeutic target in hypertension therapy. Caution should be exercised in avoiding excessively high PP values when using antihypertensive medication.

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