Heliyon 6 (2020) e03239

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Autonomic dysregulation and phenobarbital in patients with masked primary hypertension

Mustapha EL. Bakkali [a,*], Souad Aboudrar [a], Taoufiq Dakka [a], Halima Benjelloun [b]

[a] Physiology of Exercise Team and Autonomic Nervous System (PET-ANS), Faculty of Medicine and Pharmacy, University Mohammed V-Rabat, Morocco
[b] Unit of Cardiology A Ibn Sina University Hospital, Rabat 10000, Morocco

ARTICLE INFO

Keywords:
Cardiology
Physiology
Pathology
Neurology
Clinical research
Cardiovascular autonomic reflexes responses
Phenobarbital.
Masked primary hypertension
Sympathetic hyperactivity

ABSTRACT

Introduction: Primary hypertension can be masked and be responsible of a severe impact on the target bodies. The purpose of this study was to see if Phenobarbital at low dose is able to decrease the sympathetic hyperactivity assessed by cardiovascular autonomic reflexes in patients with masked hypertension.

Materials and methods: This prospective study was conducted on a total of 91 patients with masked hypertension (average age 52.1 ± 10.3 years old). The cardiovascular autonomic tests performed in this group, before and after 3 months of daily oral administration of Phenobarbital, included deep breathing, hand-grip, mental stress and orthostatic tests. Statistical analysis was done using the Student's t-test, Univariate and Multivariate logistic regression analysis; p is significant if < 0.05.

Results: Cardiovascular autonomic reflexes responses before and after 3 months of Phenobarbital oral administration were as follows: Vagal response (XDB) obtained on deep breathing test was of 32.6 ± 5.4% VS 30.4 ± 6.1%, ($p = 0.08$), alpha peripheral sympathetic response (alpha SP) obtained on hand grip test was of 35.6 ± 8.7% VS 12.0 ± 2.5%, ($p < 0.001$), alpha central sympathetic response (alpha SC), beta central sympathetic response (beta SC) obtained during mental stress were of respectively 29.3 ± 9.2% VS 11.8 ± 2.4%, ($p < 0.001$) and 11.0 ± 5.3% VS 10.4 ± 6.1%, ($p = 0.2$), alpha peripheral adrenergic sympathetic (alpha PAS) obtained during orthostatic test was of 25.3 ± 6.0% VS 13.0 ± 3.4%, ($p < 0.001$).

Conclusion: These results demonstrated that Phenobarbital at low dose may have an anti-sympathetic effect in patients with masked hypertension.

1. Introduction

Primary hypertension (HT) is the leading cause of cardiovascular morbidity and mortality worldwide. It's defined as Systolic Blood Pressure (SBP) higher than 140 mmHg and/or Diastolic Blood Pressure (DBP) higher than 90 mmHg, measured in supine position [1]. HT can be masked and be responsible of a severe impact on the target bodies. The patients whose blood pressure (BP) is normal in consultation (less than 140/90 mmHg), but exceeds the thresholds of normality by Home Blood Pressure Self-Measurement or by Ambulatory Blood Pressure Monitoring (at least 135/85 mmHg) were considered as masked hypertensive patients [2]. According to current recommendations the BP in the cabinet should be normal, it's on average 135/85 mmHg during daytime and l 120/70 mmHg during sleep in patients with MPHT [3, 4].

Masked HT (MPHT) has been proven to be associated with increased cardiovascular risk in the general population [5, 6, 7]. However, it's a frequent and poorly understood clinical form of HT but whose pathogenesis is not clear yet. The literature showed that the high sympathetic activity can be considered as a cardiovascular risk factor [8, 9]. This phenomenon has been well found in masked hypertensive patients. According to our previous study, the masked hypertensive patients showed a significant high assessed by the cardiovascular autonomic reflexes when compared to normotensive subjects [10, 11].

Otherwise, an antihypertensive treatment which reduces sympathetic nerve activity would be of an unquestionable benefit. Therefore, it is interesting to study if Phenobarbital reduces sympathetic nerve activity and thus inducing a shift in sympatho-vagal balance. The present invention relates to the field of medicine, in particular to a novel use of Phenobarbital in the treatment of autonomic dysregulation disorders. Thus, it's interesting and important to understand the mechanism of action of phenobarbital in patients with MPHT. The purpose of this study was to see if phenobarbital at small dose is able to decrease the high

* Corresponding author.
E-mail address: elbakkali78@gmail.com (M.EL. Bakkali).

https://doi.org/10.1016/j.heliyon.2020.e03239
Received 23 October 2018; Received in revised form 19 September 2019; Accepted 13 January 2020

sympathetic activity in patients with MPHT assessed by cardiovascular autonomic reflexes.

2. Materials and methods

2.1. Materials

This prospective study was conducted on a total of 91 patients with primary HT (60.5% are women and 39.5 % are men), with the average age of 52.1 years old, ranging from 25 to 76 years old.

Inclusion criteria: Patients with normal office BP and with MPHT confirmed by Home Blood Pressure Self-Measurement or by Ambulatory Blood Pressure Monitoring and during cardiovascular autonomic reflexes. The diagnosis was done after exploration of the autonomic nervous system according to the definition criteria of the masked primary hypertension.

Exclusion criteria: Patients with office hypertension were excluded from the study.

2.2. Methods

This is a prospective study comparing two cardiac autonomic evaluations: pre- and post therapeutic, carried out at the exploration unit of the autonomic nervous system (ANS), of cardiology service "A" at Ibn Sina University Hospital. The patients with BP variability attested by office BP, Home BP Self-Measurement (HBPSM) and Ambulatory BP Monitoring (ABPM) were referred to study their ANS using autonomic tests of cardiovascular reactivity in which their basal BP is normal in supine position. The study was conducted between 2016 and 2017. The study was approved by the Ibn Sina ethical committee after a thorough analysis in June 2017. A written consent form was obtained from each patient before the tests. Each patient completed a form recording the presence or absence of functional signs.

All patients received a three month treatment of 0.3–0.5 mg/kg daily oral administration of phenobarbital after the first cardiovascular autonomic testing. After this 3 months period, the second cardiac autonomic testing was performed. Phenobarbital did not have adverse reactions on patients in the study.

Tests applied on all patients included measurement of weight and height, cardiovascular autonomic tests, echocardiography and blood tests. They were also requested to go through cardiovascular examination and patients were addressed with a complete cardiac testing including electrocardiogram test and other tests when necessary as exercise test, coronary catheterization, and scintigraphy tests.

Weight and height were measured to calculate the Body Mass Index (BMI) of each subject using the usual formula weight/height 2. The result was expressed in kg/m^2.

2.2.1. Cardiovascular autonomic testing

Patients were initially lying on examination table in a quiet room for at least 30 min. The monitoring of BP, using a Dynamap (Critikon, 1846 SXP) and the Heart Rate (HR) (screen of posting LCD CS 503 E, HELLIGE, EK 512 E) was done. All the tests were applied in the morning, while patients were fasting and under no anti-hypertensive treatment during at least 48 h following the physicians' instructions.

The basal BP and HR were measured in both arms after the patients took a rest for at least 10 min. Then, the Ewing cardiovascular autonomic tests were performed.

2.2.1.1. Tests description. The cardiovascular autonomic testing included Deep Breathing (DB), Hand-Grip (HG), Mental Stress (MS) and orthostatic tests.

2.2.1.1.1. The deep breathing test (DB). This test analyzes the vagal response [12, 13]. The respiratory frequency has an influence on the variation of RR interval on the electrocardiogram (EKG). The procedure was the following: the patient breathes deeply at a frequency of six breaths for one minute [14]. It makes it possible to evaluate the vagal activity (XDB) which is expressed as a percentage:

$$(RR_{maximal} - RR_{minimal}/RR_{minimal}) \times 100$$

2.2.1.1.2. The isometric contraction or hand grip test (HG). During three minutes the patient performs a manual pressure of 50% of the maximum with assistance of a dynamometer. The muscular contraction involves a rise in BP related to an increase of sympathetic nerve activity at the muscular level which is effort-dependent and time-dependent [15, 16]. The peripheral alpha sympathetic nerve response is given by the increase of the BP.

The alpha peripheral sympathetic response (alpha PS) is performed as bellow:

$$= (BP_{after\ the\ test} - BP_{before\ the\ test}/\ BP_{before\ the\ test}) \times 100$$

2.2.1.1.3. The mental stress test (SM). The patient performs mental arithmetic calculations by removing the number 7 successively from 200. The result is an increase in BP and in HR by the central sympathetic nerve activation [14]. In mental stress, the central sympathetic nerve activity "α" was evaluated by measuring the variations of BP as bellow [15, 16].

Alpha central sympathetic response (alpha CS)

$$= (BP_{after\ stimulation} - BP_{before\ stimulation}/BP_{before\ stimulation}) \times 100$$

The "β" central sympathetic nerves activities was evaluated by measuring the variations of

HR as bellow [15, 16].

Beta central sympathetic response (beta CS)

$$= (HR_{after\ stimulation} - HR_{before\ stimulation}/HR_{before\ stimulation}) \text{ x } 100$$

2.2.1.1.4. The orthostatic test (OT). The OT is a simple, non invasive and reproducible test among the cardiovascular ANS tests, involving the measurement of the BP and the HR variation during standing position [17]. The basal BP and HR were measured in both arms after a rest of at least 10 min in supine position. Then the OT was proceeded. Orthostatic BP and HR were recorded for 10 min at the rhythm of 3 measurements per minute. In this study, only the BP values were analyzed. Orthostatic HT is defined by an increase in the systolic BP of at least 20 mmHg and/or in the diastolic BP (DBP) of at least 10 mmHg during standing position or even as SBP higher than 150 mmHg and/or DBP higher than 100 mmHg in standing position.

The alpha peripheral adrenergic sympathetic response (Alpha PAS) obtained during the OT was evaluated by measuring the variations of BP as bellow:

$$= (BP_{orthostatic} - BP_{supine\ position}/BP_{supine\ position}) \times 100$$

The results of the peripheral sympathetic response are expressed as percentage.

2.2.2. Echocardiographic detection

Pathological hypertrophy may be associated with an absence of symptoms for many years

before the development of congestive heart failure or unexpected sudden death. Thus, in contemporary clinical practice and population studies, the diagnosis of LVH depends predominantly on echocardiographic measurements or novel noninvasive imaging techniques.

Methods for 2D targeted M-mode echocardiographic measurements of Left Ventricule (LV) dimensions and the calculation of LV mass are standardized [18]. The detection of pathological LVH requires adjustments for sex, height, and body mass.

Echocardiographic measurements were performed in accordance with the American Society of Echocardiography, and the calculation of LV Mass (LVM) was done using the modified formula of:

$$LVM\ (g) = 0.8 \times [1.04 \times (LVID + LVPWT + IVST)^3 – LVID^3]] + 0.6$$

Where LVID indicates LV Internal Diameter; LVPWT indicates LV Posterior Wall Thickness; and IVST indicates IntraVentricular SeptalTthickness [19].

2.3. Statistical analysis

Descriptive statistics included the range, mean, and standard deviation for interval variables and the frequency and percentage for categorical variables. Group comparisons were carried out by independent samples Student's t-test for interval variables and the $\chi 2$ test for categorical variables, with 95% confidence intervals (CIs) calculated where appropriate. Univariate and multivariate logistic regression analysis were performed to assess the independent association of several variables with MPHT. These effects were measured by odds ratios (OR), and their 95% CIs based on logistic regression models. p values were 2 sided and were considered statistically significant if less than 0.05. All analyses were performed using SPSS, version 15.0 (SPSS Inc., Chicago, Il).

3. Results

In this population, supine average basal HR was of 67.2 ± 6.4 beats/min (with the extreme ranging from 63 to 74 beats/min). Supine average basal SBP and overage basal DBP were respectively 120.6 ± 6.1mmHg (with the extreme ranging from 118 to 124 mmHg) and 80.4 ± 11.6mmHg (with the extreme ranging from 74 to 87 mmHg) (see Table 1).

Cardiovascular autonomic reflexes responses before and after phenobarbital treatment were respectively as follows: vagal response (XDB) obtained during DB was of 32.6 ± 5.4% vs 30.4 ± 6.1%, p = 0.08 (Table 2), alpha peripheral sympathetic response (Alpha PS) obtained on HG test was of 35.6 ± 8.7% vs 12.0 ± 2.5%, p < 0.001 (Table 2; Figure 1), alpha central sympathetic response (Alpha CS) obtained during MS was of 29.3 ± 9.2% vs 11.8 ± 2.4, p < 0.001 (Table 2; Figure 1), beta central sympathetic response (Beta CS) obtained during MS was of 11.0 ± 5.3% vs 10.4 ± 6.115.8 ± 3.4% (p = 0.2). Alpha peripheral adrenergic sympathetic response (Alpha PAS) obtained during OT was of 25.3 ± 6.0% vs 13.0 ± 3.4%, p < 0.001 (Table 2; Figure 1).

Also, in the present study we were interested in investigating the kinetics orthostatic BP in this population during the change from supine position to standing position and during standing position before and after phenobarbital treatment (Figure 2). Only the SBP values were analyzed.

In addition, the OT showed a significant decrease in the orthostatic SBP at each time of this test in comparison to the orthostatic SBP values obtained before phenobarbital treatment (Figure 2).

Table 1. Baseline characteristics of patients.

Parameters	Values
Age (year)	52.1 ± 10.3
Sex (F/M)	55(60.5%)/36(39.5%)
Basal SBP (mmHg)	120.6 ± 6.1
Basal DBP (mmHg)	80.4 ± 11.6
Basal HR (beats/min)	67.2 ± 6.4
LVEF (%)	59
BMI (kg/m^2)	29.5 ± 3.7

SBP: Systolic Blood Pressure.
DBP: Diastolic Blood Pressure.
HR: Heart Rate.
LVEF: Left Ventricular Ejection Fraction.
BMI: Body Mass Index.
Values were expressed as average ±SE, and as effective (percentage).

Table 2. Vagal response on deep breathing test (XDB). Alpha peripheral sympathetic response (alpha SP) obtained on hand grip test. Alpha central sympathetic response (alpha SC), beta central sympathetic response (beta SC) obtained during mental stress, and alpha peripheral adrenergic sympathetic (alpha PAS). Parameters were measured before and after treatment by phenobarbital, and expressed as average ± SE; **: p < 0.05.

Test	XDB (DB)	alpha PS (HG)	alpha CS (MS)	beta CS (MS)	alpha PAS (OT)
Before phenobarbital treatment	32.6 ± 5.4	35.6 ± 8.7	29.3 ± 9.2	11.0 ± 5.3	25.3 ± 6.0
After phenobarbital treatment	30.4 ± 6.1	12.0 ± 2.5**	11.8 ± 2.4**	10.4 ± 6.1	13.0 ± 3.4**

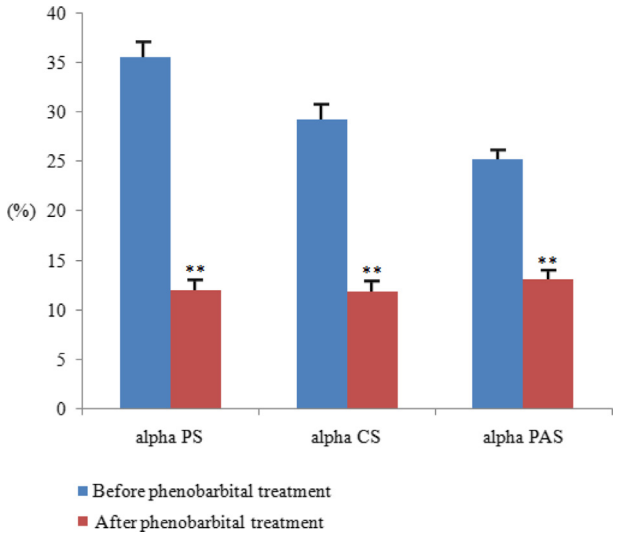

Figure 1. Alpha peripheral sympathetic response (alpha PS) obtained on hand grip test, alpha central sympathetic response (alpha SC) obtained during mental stress, and alpha peripheral adrenergic sympathetic response (alpha PAS) obtained during orthostatic test. Parameters were measured before and after treatment by phenobarbital and expressed as average ± SE; **: P < 0.05.

For example, at the 5th and 10th minutes of OT, the orthostatic SBP decreased by 41 mmHg and 57 mmHg respectively in comparison to the orthostatic SBP values obtained in the same time of OT before phenobarbital treatment (Figure 2).

3.1. Logistic regression analysis

Univariate logistic regression analysis showed that the odds of MPHT increased with alpha peripheral sympathetic response (Alpha PS) (OR = 2.401, 95% CI: 1.701–5.039, p = 0.003), alpha central sympathetic response (Alpha CS) (OR = 2.010, 95% CI: 1.106–4.008, p = 0.002), and Alpha peripheral adrenergic sympathetic response (Alpha PAS) (OR = 2.307, 95% CI: 1.106–4.008, P = 0.006) respectively, in patients with MPHT. On the other hand, the odds of MPHT decreased with phenobarbital treatment (OR = 0.158, 95% CI: 0.326–0.615, p < 0.001) in patients with MPHT.

Multivariate logistic regression analysis showed that the same independent factors were associated with MPHT. The odds of MPHT increased with Alpha PS (OR = 1.507, 95% CI: 1.381–3.018, p = 0.024), Alpha CS (OR = 2.0802, 95% CI: 1.906–5.078, p = 0.03), and Alpha PAS (OR = 1.159, 95% CI: 1.131–2.069, p = 0.02) respectively, in patients with MPHT. However, the odds of MPHT decreased with phenobarbital treatment (OR = 0.217, 95% CI: 0.406–0.735], p < 0.001) in patients with MPHT.

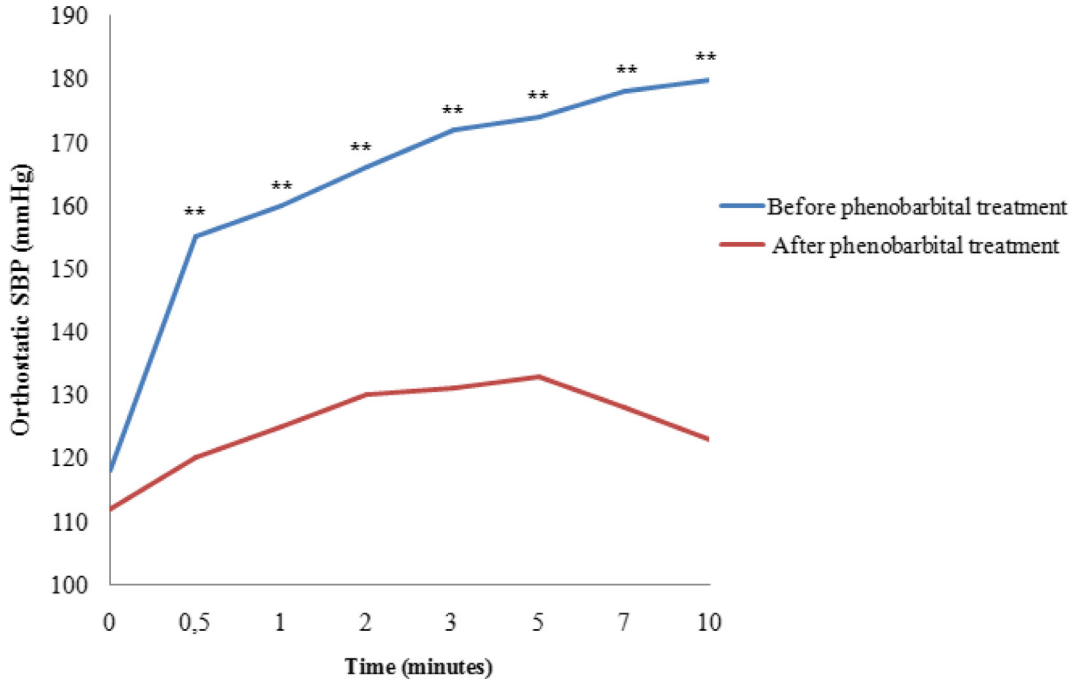

Figure 2. Representative curve of the kinetics of the Mean SBP in patients with masked orthostatic hypertension during orthostatic test before and after treatment (**: $P < 0.05$).

4. Discussion

Masked HT is a clinical phenomenon that is becoming increasingly important and its prevalence of the order of 8–30% demonstrates the importance of being interested [2, 20]. This high variability of prevalence of masked HT within these previous studies potentially could be due to the heterogeneity of populations and the procedure of BP measurement [21].

Masked HT (MPHT) is a frequent and poorly understood clinical form of HT but which pathogenesis is not clear yet. The literature showed that the high sympathetic activity can be considered as a cardiovascular risk factor [8, 9]. This phenomenon has been well found in primary hypertensive patients, especially in patients with MPHT. The purpose of this study was to see if Phenobarbital in small dose is able to decrease the sympathetic hyperactivity assessed by cardiovascular autonomic reflexes in patients with MPHT.

The cardiovascular ANS reflexes which include the measurement of the sympathetic and vagal nerve activity are considered now among the most effective clinical tests. Thus, in a previous study, we compared the autonomic cardiovascular reflexes of a group of masked hypertensive patients with a group of normotensive subjects [10] and we reported that sympathetic response was significantly higher and the vagal response was not significantly different in masked hypertensive patients when compared to normotensive subjects.

Autonomic dysregulation plays a significant role in HT and acts as a coronary risk factor by severe metabolic complications [22]. In a previous study, the microneurography has shown the increased activity of the sympathetic fibers specifically proportional to the severity of the HT, but not that of secondary HT. This could help to explain why some metabolic risk factors and some common diseases related with essential HT are not found in secondary HT. Mancia G and al showed that in hypertensive patients, the overactivation of the Sympathetic Nervous System (SNS) could be dependent on the circulating angiotensin II concentrations, because angiotensin II exerts excitatory effects on sympathetic outflow, to facilitate norepinephrine release from adrenergic nerve endings, and to amplify adrenergic receptor responsiveness to stimuli [17]. Previous papers showed that spectral analysis techniques provided important information regarding the alterations of the nervous control of HT and allowed an increase in sympathetic activity [23, 24].

Otherwise, in the present study, our interest was the focus on Phenobarbital mechanism in patients with MPHT. Thus, the study of the cardiovascular autonomic profile under a new antihypertensive molecule such as phenobarbital was interesting. The analysis of the results demonstrated that cardiovascular autonomic reflexes showed a significant reduction of the sympathetic hyperactivity in patients with MPHT. These data showed the relationship between MPHT and sympathetic hyperactivity in these masked hypertensive patients.

It was significantly higher in hypertensive patients before the three months of treatment with Phenobarbital.

In addition, a univariate and multivariate logistic regression analysis was performed in the present study to determine independent predictor factors of MPHT in the patients whose MPHT was detected. The analysis of the results indicates that some independent predictor factors, such as age, sympathetic hyperactivity and treatment with Phenobarbital were significantly associated with HT respectively, in patients with MPHT (Table 3). These data suggested that there is a positive linear association between the occurrence of MPHT and sympathetic hyperactivity (table). Also, the results of the present study demonstrated that there is an increase in the occurrence of MPHT with the age of the subject in whom the MPHT has been detected. This finding has been confirmed by a previous study conducted by Trudel X et al that the prevalence increased with age [2]. On the other hand, in our study there is a negative linear association between the occurrence of MPHT and the treatment with Phenobarbital (Table 3). This data indicated that there is a relationship between the reduction in the occurrence of MPHT and the treatment with Phenobarbital. Hence, our interest in this study was to demonstrate the reduction of sympathetic hyperactivity, thus the reduction in cardiovascular risk using this new therapeutic molecule in those patients.

In our study, the use of phenobarbital in a small dose in the treatment of autonomic dysregulation disorders in primary hypertensive patients showed a significant effect on the sympathetic nervous system. As a result, the long-term treatment reduces the sympathetic hyperactivity encountered during tests for stimulating the sympathetic system.

Table 3. Evaluation of relationship between masque HT and independent predictor factors by univariate and multivariate logistic regression analyses; *: p significative if < 0.05.

	Univariate analysis			Multivariate analysis		
Parameters	Odds ratios (OR)	95% CI	p	Odds ratios (OR)	95% CI	p
Age (year)	2.210	[1.012–3.253]	0.02*	1.316	[1.014–2.903]	0.03*
Range (years)	1.815	[1.063–2.480]	0.03*	2.013	[1.177–3.086]	0.04*
Sex (F/M)	0.313	[0.171–1.907]	0.6			
LVM (g)	0.914	[0.358–3.983]	0.8			
IVST (mm)	0.522	[0.410–2.054]	0.7			
BMI (kg/m^2)	1.016	[0.776–2.106]	0.6			
XDB (%)	0.719	[0.210–2.060]	0.4			
Alpha PS (%)	2.401	[1.701–5.039]	0.003*	1.507	[1.381–3.018]	0.024*
Alpha CS (%)	2.010	[1.106–4.008]	0.002*	2.080	[1.906–5.078]	0.03*
Beta CS (%)	0.975	[0.102–2.804]	0.1			
Alpha PAS (%)	2.307	[1.405–3.193]	0.006*	1.159	[1.131–2.069]	0.02*
Phenobarbital (mg/kg)	0.158	[0.326–0.615]	0.0001*	0.217	[0.406–0.735]	0.0001*

Accordingly, a univariate and multivariate logistic regression analysis showed that LVM and IVST were not significantly associated with MPHT respectively in patients with MPHT (Table 3). However, a previous study demonstrated that LVM significantly increased in subjects with masked HT compared to normotensive subjects. These observations were confirmed in a much larger sample of the population (PAMELA study) [25].

This is the first study to demonstrate that Phenobarbital is associated with potentially beneficial effects on the sympathetic activity in patients with MPHT.

All in all, it would be interesting to conduct a further study focusing on a direct comparison that will include all the cardiovascular ANS tests between patients within MPHT under the treatment with phenobarbital, patients with sustained HT and normotensive patients to understand the mechanisms of action of this new therapeutic molecule.

5. Conclusion

The results of this study demonstrated that in masked hypertensive patients, the use of phenobarbital in a small dose showed a significant decrease of the high sympathetic activity assessed by cardiovascular autonomic reflexes. Thus, the novel pharmacological prescription reduces the intensity of the essentially neurosensory and cardiovascular functional symptomatology suffered by the patient. In fact, high interest has to be giving to cardiovascular autonomic reflexes and treatment by phenobarbital must be studding at large scale.

Declarations

Author contribution statement

Mustapha El Bakkali: Conceived and designed the experiments; Performed the experiments; Wrote the paper.

Souad Aboudrar, Halima Benjelloun: Analyzed and interpreted the data.

Taoufiq Dakka: Contributed reagents, materials, analysis tools or data.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

Acknowledgements

We thank Professor Halima Benjelloun for her assistance with technical guidance.

References

[1] O.A. Carretero, S. Oparil, Essential hypertension. Part I: definition and etiology, Circulation 101 (2000) 329–335.
[2] X. Trudel, C. Brisson, B. Larocque, A. Milot, Masked hypertension: different blood pressure measurement methodology and risk factors in a working population, J. Hypertens. 27 (2009) 1560–1567.
[3] J.A. Staessen, L. Beilin, G. Parati, et al., Task force IV: clinical use of ambulatory blood pressure monitoring, in: Participants of the 1999 Consensus Conference on Ambulatory Blood Pressure Monitoring 4, Blood Press Monit, 1999, pp. 319–331.
[4] European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension, J. Hypertens. 21 (2003) 1011–1053.
[5] G. Mancia, et al., Long-term risk of mortality associated with selective and combined elevation in office, home, and ambulatory blood pressure, Hypertension 47 (2006) 846–853.
[6] R.H. Fagard, V.A. Cornelissen, Incidence of cardiovascular events in white-coat, masked and sustained hypertension versus true normotension: a meta-analysis, J. Hypertens. 25 (2007) 2193–2198.
[7] Wenjin Liu, Liang Wang, Zhuxing Sun, et al., Masked uncontrolled hypertension in patients on maintenance hemodialysis, Hypertens. Res. 40 (2017) 819–824.
[8] S.S. Franklin, S.A. Khan, N.D. Wong, et al., Is pulse pressure useful in predicting risk for coronary heart Disease? The Framingham heart study, Circulation 100 (1999) 354–360.
[9] J.E. Muller, G.H. Tofler, R.L. Verrier, Sympathetic activity as the cause of the morning increase in cardiac events: a likely culprit, but the evidence remains circumstantial, Circulation 91 (1995) 2508–2509.
[10] M. EL Bakkali, T. Dakka, L. Coghlan, et al., Contribution to masked hypertension understanding: role of autonomic cardiovascular tests, World J. Pharm. Res. 4 (2015) 54–68.
[11] M. Giuseppe, G. Guido, The autonomic nervous system and hypertension, Circ. Res. 114 (2014) 1804–1814.
[12] D.J. Ewing, C.M. Martyn, R.J. Young, et al., The value of cardiovascular autonomic function tests: 10 years experience in diabetes, Diabetes Care 8 (1985) 491–493.
[13] D.J. Ewing, J.B. Irving, F. Kerr, et al., Cardiovascular responses to sustained handgrip in normal subjects and in patients with diabetes mellitus: a test of autonomic function, Clin. Sci. Mol. Med. 46 (1974) 295–306.
[14] P.A. Low, Laboratory evaluation of autonomic function, in: P.A. Low (Ed.), Clinical Autonomic Disorders. Evaluation and Managment, second ed., Lippincott-Raven, Philadelphia, 1997, pp. 179–208.
[15] H.C. Coghlan, Orthostatic intolerance: mitral valve prolapse, in: D. Robertson, P.A. Low, J. Polinsky (Eds.), Primer on the Autonomic Nervous System, Academic Press, San Diego, California, 1996, pp. 283–286.
[16] T.L. Ohansen, G. Kambskar, Mehlsen, J Heart rate variability in evaluation of the autonomic nervous system, Ugeskr. Laeger 159 (1997) 6666–6671.
[17] P.A. Low, M.A. Pfeifer, Standardization of autonomic function, in: P.A. Low (Ed.), Clinical Autonomic Disorders, second ed., Lippincott-Raven, 1997, pp. 287–295.
[18] C. Vuille, A.E. Weyman, Left ventricle: general considerations, assessment of chamber size and function, in: A.E. Weyman (Ed.), Prin- ciples and Practice of

Echocardiography, second ed., Lea & Febiger, Philadelphia, Pa, 1994, pp. 575–620.
[19] D. Levy, D.D. Savage, R.J. Garrison, et al., Echocardiographic criteria for left ventricular hypertrophy: the Framingham Heart Study, Am. J. Cardiol. 59 (1987) 956–960.
[20] G.T. Pickering, K. Eguchi, K. Kario, Masked hypertension: a review, Hypertens. Res. 30 (2007) 479–488.
[21] G.S. Stergiou, E.V. Salgami, D.G. Tzamouranis, et al., Masked hypertension assessed by ambulatory blood pressure versus home blood pressure monitoring: is it the same phenomenon? Am. J. Hypertens. 1 (2005) 772–778.
[22] K. Miwa, A. Igawa, Y. Miyagi, et al., Alterations of autonomic nervous activity preceding nocturnal variant angina: sympathetic augmentation with parasympathetic impairment, Am. Heart J. 135 (1998) 762–771.
[23] M. Pagani, D. Lucini, Autonomic dysregulation in essential hypertension: insight from heart rate and arterial pressure variability, Auton. Neurosci. 90 (2001) 76–82.
[24] M. Esler, The sympathetic system and hypertension, Am. J. Hypertens. 13 (2000) 99–105.
[25] R. Sega, G. Trocino, A. Lanzarotti, et al., Alterations of cardiac structure in patients with isolated office, ambulatory, or home hypertension: data from the general population (Pressione Arteriose Monitorate E Loro Associazioni (PAMELA) Study), Circulation 104 (2001) 1385–1392.