The OXIMAPA Study: Hypertension Control by ABPM and Association with Sleep Apnea Syndrome by Pulse Oximetry

Estudo OXIMAPA: Controlo da Hipertensão por MAPA e Associação com Síndrome da Apneia do Sono por Oximetria

ARTIGO ORIGINAL

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Acta Med Port 2017 Feb;30(2):93-99 ▪ http://dx.doi.org/10.20344/amp.7495

ABSTRACT

Introduction: Ambulatory blood pressure monitoring by automatic device is the best blood pressure evaluation method and sleep apnea syndrome is the leading cause of poor control. Oximetry allows screening these individuals but its usefulness has been poorly explored in Primary Health Care. The aim was to evaluate the blood pressure control at the office and with ambulatory blood pressure monitoring by automatic device and to relate it to sleep apnea syndrome.

Material and Methods: We selected a sample of 50 participants, representative of 3036 hypertensive patients. The variables were: blood pressure value at the office and blood pressure with ambulatory blood pressure monitoring by automatic device; presence of criteria of sleep apnea syndrome in oximetry.

Results: The prevalence of uncontrolled blood pressure was 56% on office evaluation and 68% on ambulatory blood pressure monitoring by automatic device. It was found: 36% of daytime hypertension, 52% nocturnal hypertension, 40% non-dipper profile, 16% of white coat hypertension and 28% masked hypertension. The prevalence of sleep apnea syndrome was 16%. Blood pressure in ambulatory blood pressure monitoring by automatic device and blood pressure in office showed no statistically significant association (p = 0.761). We found a statistically significant association between sleep apnea syndrome and daytime hypertension (p = 0.019) and non-dipper profile (p = 0.005).

Discussion and Conclusion: Ambulatory blood pressure monitoring by automatic device detected more 12% of uncontrolled hypertension than office blood pressure. Sleep apnea syndrome is strongly associated with uncontrolled hypertension and oximetry may be a good screening method, but should be studied further.

Keywords: Blood Pressure Monitoring, Ambulatory; Hypertension; Oximetry; Sleep Apnea Syndromes

RESUMO

Introdução: A monitorização ambulatorial da pressão arterial é o melhor método de avaliação da pressão arterial e a síndrome da apneia do sono é a principal causa de mau controlo. A oximetria permite rastrear estes indivíduos mas a sua utilidade tem sido pouco explorada em Cuidados de Saúde Primários. O objectivo foi avaliar o controlo da pressão arterial no consultório e na monitorização ambulatorial da pressão arterial, e relacioná-la com a síndrome da apneia do sono.

Material e Métodos: Selecionou-se uma amostra de 50 participantes, representativa de 3036 doentes hipertensos. As variáveis avaliadas foram: valor de pressão arterial no consultório e na monitorização ambulatorial da pressão arterial; presença de critérios de síndrome da apneia do sono na oximetria.

Resultados: A prevalência de pressão arterial não controlada foi de 56% no consultório e 68% na monitorização ambulatorial da pressão arterial. Encontrou-se: 36% de hipertensão diurna, 52% de hipertensão nocturna, 40% de perfil não-*dipper*, 16% de hipertensão da bata-branca e 28% de hipertensão mascarada. A prevalência de síndrome da apneia do sono foi 16%. A pressão arterial no consultório e na monitorização ambulatorial da pressão arterial não mostrou associação estatisticamente significativa (p = 0,761). Encontrou-se uma associação estatisticamente significativa entre síndrome de apneia do sono e hipertensão diurna (p = 0,019) e perfil não-*dipper* (p = 0,005).

Discussão e Conclusão: A monitorização ambulatorial da pressão arterial detetou mais 12% de casos de hipertensão não controlada do que o consultório. A síndrome da apneia do sono está fortemente associada a hipertensão não controlada e a oximetria pode ser um bom método de rastreio, mas deve ser mais estudada.

Palavras-chave: Hipertensão; Monitorização Ambulatória da Pressão Arterial; Oximetria; Síndromes da Apneia do Sono

INTRODUCTION

High blood pressure (HBP) is a disease with great worldwide prevalence and incidence, contributing significantly towards high morbidity and mortality in developed countries. Stroke is the leading cause of death in Portugal, probably due to the reduced control of blood pressure (BP)[1] and high salt intake.[2] According to Portuguese data it is estimated that approximately 42% of the population is hypertensive.[3,4] Among the diagnosed hypertensive patients the adherence rate reaches 84.8%,[3] but only between 28.6% and 42.5% of these are controlled.[3,4]

Addressing the HBP has been a challenge once the less typical presentations create difficulties in diagnosis and control. An example is the white coat hypertension, it is found in 20% to 70% of the diagnosed and treated patients.[5] In other patients the nocturnal BP seems to be controlled but they do not exhibit the physiological decrease expected

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Recebido: 07 de fevereiro de 2016 - Aceite: 22 de agosto de 2016 | Copyright © Ordem dos Médicos 2017

during nighttime, which, in healthy individuals with lower cardiovascular risk (CVR), is generally about 10% to 20% of the daytime values. This phenomenon affects up to 25% of the general population,[6] but it can reach even more in some specific sub-groups, such as obese children.[7] This is the non-dipper profile and its prevalence in hypertensive patients can reach 60% in primary care.[8] The nocturnal BP represents the greatest prognostic value for CVR[9,10] and in all these atypical forms of presentation this risk increases.[11-17]

There are several available techniques for the hypertension diagnosis and control, including the evaluation in medical office, ambulatory self-measurement and ambulatory blood pressure monitoring by automatic device (ABPM). Several studies and international guidelines refer to the ABPM as an essential tool in the evaluation and control of hypertension, and therefore it is a good indicator of cardiovascular risk, exhibiting the best efficacy and cost-effectiveness,[18-20] including in the Portuguese population.[21] Some authors reinforced its importance in the Primary Health Care (PHC) by suggesting that it should be available for family doctors' use.[22,23]

Several studies attempted to elucidate the mechanisms underlying resistant HBP and its different types of presentation, and obstructive sleep apnea syndrome (SAS) is possibly the main secondary cause, especially the obstructive form which may occur in about 80% of the patients.[24,25] SAS is often asymptomatic and the global prevalence can reach 30%. There is a strong association between SAS and daytime high blood pressure, nocturnal HBP and non-dipper profile.[24-26] It is one of the main predictors of increased CVR in patients with HBP, and the pathophysiological mechanism may be through hypoxemia phenomenon.[24-26] Polysomnography (PSG) is the best test for diagnosing sleep apnea syndrome, especially to distinguish between obstructive and central form, however, due to its limited availability in PHC, the nocturnal pulse oximetry is recommended as a great method to screen these patients. It achieves sensitivity up to 98% and some evidence of its validity is emerging.[27-32] The European Respiratory Society also recommends an evaluation with ABPM in hypertensive patients showing obstructive apnea.[32] Despite being well explored in Secondary Health Care, few studies were performed in the Portuguese Primary Health Care to assess the utility of ambulatory blood pressure monitoring by automatic device in the control of hypertensive patients, as well as the association between HBP and sleep apnea syndrome.

The aim of this study was to describe the hypertensive population of a Portuguese Health Centre unit regarding the control of blood pressure, either through ABPM and office evaluation, and to relate different profiles of uncontrolled HBP with sleep apnea syndrome, screened by nocturnal pulse oximetry.

MATERIAL AND METHODS

Study design

An observational, descriptive and analytical study was carried out in a Portuguese health center unit of Aveiro. Inclusion criteria were: adult patients diagnosed with hypertension (with or without complications) and treated with, at least, one class of antihypertensive drugs. Exclusion criteria were: non-adherence to antihypertensive therapy during the study conduction or in the previous three weeks, clinical severe acute condition and the use of noninvasive breathing assistance device. It was applied a case-control design for the data analysis. All participants signed an informed consent.

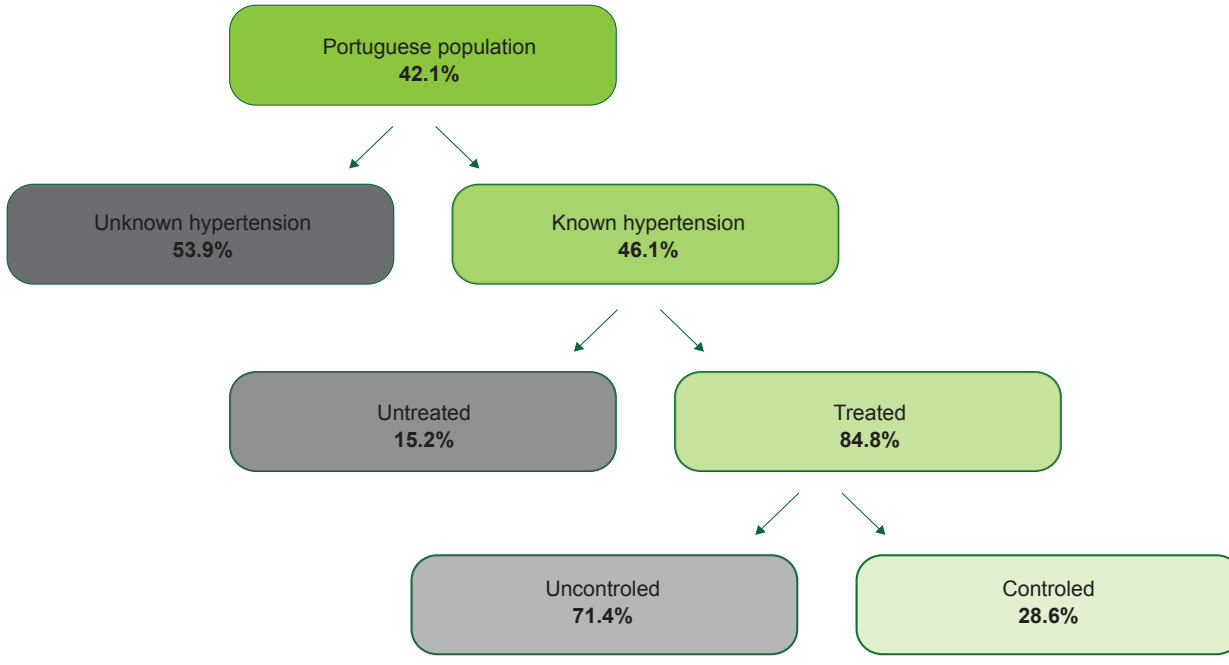

Figure 1 – Epidemiologic prevalence data of hypertension in Portugal (data adapted from Barros P et al, 2007)[1]

Sample size assessment

A statistically representative sample was calculated, set from a target population of 3036 hypertensive individuals registered in the Aveiro health center. To ensure the statistical representativeness of the sample, we used the online free access tool EpiInfo (*weblink:* www.openepi.com) to calculate it and all participants were selected by simple random sampling with replacement. Individuals with controlled HBP were considered as 'control', with an estimated prevalence of 28.6% among treated patients, and as 'cases', individuals with poorly controlled HBP, estimated in 71.4%. These prevalence rates were used to sample size calculation. A 95% confidence interval with β value (power) of 80% and a ratio of cases/controls of 1:1 were established. At last, the sample size was readjusted for excess, considering the estimated proportion of adherence and full compliance of the study (70% default), as well as treatment adherence (84.8% of patients diagnosed with HBP). Fig. 1 summarizes the epidemiological data for the Portuguese population[1] considered in this calculation and Fig. 2 shows the used mathematical equation to the sample size readjustment, estimating a complete sample size of 89 individuals. Table 1 summarizes baseline characteristics and the participants selection process.

$$n = \frac{n0}{p1 \times p2}$$

n: Readjusted final sample size;
n0: Sample size initially calculated;
p1: Fraction of treatment adherence (0.848);
p2: Fraction of adherence and full compliance with the study (0.7)

Figure 2 – Adjusted sample size calculation formula

Variables

Three nominal qualitative variables were defined: the evaluation of BP in the office; BP using the ABPM; and the presence of SAS criteria in oximetry. Table 2 shows the maximum BP values considered normal for the control group, as well as the values of the oxygen desaturation index - ODI (average number of desaturation events per hour, during 10 seconds each). For ODI values two cutoff points were used, one was representing 100% sensitivity for the diagnosis of SAS and the other one was representing 100% specificity for its exclusion. Therefore, by setting these cutoff points, it is statistically implied the rational presumption of diagnosis, either for its confirmation or exclusion. However, all the intermediate results that did not fulfill these criteria were defined as uncertain for the diagnosis of SAS. Thus, three different profiles were defined: positive, uncertain, and negative oximetry results for SAS. It was not assessed the presence of symptoms or clinical findings suggestive of SAS. Different HBP profiles were also defined:

Table 1 - Description of baseline characteristics and the participants' selection

Target Population (Hypertensive patients registered in the Aveiro Health Center unit by July 2013)	3036
Number of participants randomized and invited to participate	89
Number of excluded participants	39
Do not attended or did not fulfill inclusion criteria	15
Missed the scheduled date or rejected to participate	24
Number of obtained participants	50
Baseline Characteristics	
Males (%)	50
Mean Age (± sd)	63.48 (± 11.11)
Mean BMI (± sd)	29.37 (± 4.64)

BMI: Body Mass Index (Kg/m^2)

Table 2 - Criteria defined to the operationalization of variables studied

		Systolic BP (mmHg)*	Diastolic BP (mmHg)*
Office		140	90
ABPM	**Global (24h)**	130	80
	Day time (07 - 23h)	135	85
	Night time (23 - 07h)	120	70
ODI			
Oximetry	**Positive**	If superior than 32 for decreases of 3% in O_2Sat OR superior than 4.3 for decreases of 5% in O_2Sat	
	Uncertain	Intermediate values	
	Negative	If inferior than 12.2 for decreases of 2% in O_2Sat	

ODI: Oxygen desaturation index (events/hour); O_2Sat: Oxygen pulse saturation in %
* The values refer to the average blood pressure (BP) obtained and define the maximum limits to consider the variable as 'controlled'

daytime, nocturnal, masked, white coat and non-dipper. The limits to define uncontrolled BP were set for BP according to the guidelines of the National Institute for Health and Clinical Excellence, 2011,[20] the European Society of Hypertension (ESH), 2005[33] and the Portuguese clinical guideline of the General Health Directorate (DGS) 020/2011 for HBP.[34] Although there are different concepts of 'uncontrolled HBP' (BP levels above 140/90 mmHg regardless the number of drugs and secondary causes) and 'resistant HBP' (BP levels above 140/90 mmHg despite taking three different drugs),[25] we did not use any classification to differentiate participants. The guidelines followed to evaluate the oximetry were set by the American Academy of Sleep Medicine 2012,[31] the European Respiratory Society 2013[32] and the oximeter validation study.[35] ABPM was performed in a regular active day for a period of 24 hours through the validated SPACELABS HEALTHCARE® device, model 90217A,[36] in the same arm on which the office evaluation was performed. The oximetry was collected using a finger sensor and performed through the validated device WristOx®, model 3150SK-04.[35] The office BP values were obtained in two moments, one before and the other after the implementation of the ABPM device. A minimum of three measurements on each day were taken and the first measurement of each one was excluded. The final used value was the arithmetic average of the remaining four measurements.

Data were analyzed using IBM SPSS Statistics 20®. Descriptive statistics were used to calculate the HBP and the SAS prevalence and analytical tests were used for the different variables association. The quantitative variables were tested for normal distribution using Kolmogorov-Smirnov and compared using One-way ANOVA test. The qualitative variables are presented in contingency table, using the Fisher's exact test and calculating the odds ratio (OR).

RESULTS

Fifty volunteers participated in the study, 25 (50%) women and 25 (50%) men with a mean age of 63.48 (± 11.11) years and mean body mass index (BMI) of 29.37 (± 4.64) kg/m^2. Regarding the anti-hypertensive drug classes, 22 (44%) participants were treated with diuretics, 22 (44%) with angiotensin converting enzyme inhibitor, 19 (38%) with angiotensin receptor antagonist, 14 (28%) with calcium channel antagonist, four (8%) with a beta blocker, one (2%) with a nitrate and one (2%) with an alpha blocker. Twenty two (44%) patients were treated with only one drug, 23 (46%) with two drugs and five (10%) with three drugs. There were no significant differences in BMI between different groups of oximetry results (p = 0.09, independent samples t test).

Table 3 - Prevalence results of different profiles found in office BP, ABPM and Oximetry [in % (No.)]

	Office	ABPM
Controlled HBP	44% (22)	32% (16)
Uncontrolled HBP	56% (28)	68% (34)
Daytime HBP		36% (18)
Nocturnal HBP		52% (26)
Non-dipper profile		40% (20)
White coat HBP		16% (8)
Masked HBP		28% (14)
	Oximetry	
Positive criteria for SAS	16% (8)	
Uncertain criteria for SAS	16% (8)	
Negative criteria for SAS	68% (34)	

ABPM: Ambulatory blood pressure monitoring; HBP: High blood pressure; SAS: Sleep apnea syndrome

The oximetry results and the prevalence of different BP profiles obtained in the office evaluation and ABPM are in Table 3. In addition to the eight (16%) patients with positive criteria in oximetry for diagnosis of SAS, eight more participants showed uncertain results, however they were not included in the statistical tests for the association of these variables.

Contingency Table 4 shows the results of the BP assessment in ABPM and office and no significant association was found between them (p = 0.76, Fisher's exact test). Table 5 shows the association between SAS and the several blood pressure profiles in HBPM. Despite no statistically significant association was found between SAS and nocturnal high blood pressure, among the 20 participants with nocturnal HBP, nine of them reported poor sleep quality, and in fact, after exclusion of these cases this association acquires a statistical significance (p = 0.049, Fisher's exact test). There was also an association between SAS and daytime HBP and non-dipper profile, respectively, with statistically significant associations found (p = 0.019 and p = 0.005 respectively, Fisher's exact test).

Table 6 shows the mean BP levels (in office and in ABPM) and the mean % of nocturnal dipping, between the various groups of oximetry results. There were found significant differences between the three groups in the global systolic blood pressure in ABPM and in the mean % of nocturnal dipping, suggesting that the SAS group have worse parameters. These findings are consistent with the previous ones, when these variables were converted in quantitative set. Despite this, the same relationship was not found between diastolic BP values and SAS.

DISCUSSION AND CONCLUSION

HBP profiles and control

In this study, the prevalence of uncontrolled HBP was 68%, similar to that reported in the Portuguese literature, which is between 57.5% and 71.4%.[3,4] Among its different profiles, the prevalence of white coat HBP (16%) was slightly below other bibliographic reports, between 20 and 70%.[5] Regarding this fact, although some researchers suggest an association with higher CVR, the controversy on the benefit of treating such patients remains.[37] In our study, the prevalence of non-dipper profile (40%) was similar to the ones reported in other surveys (between 25% to 60%).[6,7] The occurrence of masked HBP (28% in our study) was relatively high, revealing the cases that are

Table 4 - Association between BP measurement in ABPM and in office

		BP in ABPM		Total
		Uncontrolled	Controlled	
BP in Office	**Uncontrolled**	20	8	28
	Controlled	14	8	22
Total		34	16	50

Fisher`s exact test: $p = 0.761$; Odds ratio = 1.43
ABPM: Ambulatory blood pressure monitoring; BP: Blood pressure

Table 5 - Association between SAS and: nocturnal HBP, Daytime HBP and non-dipper profile.

		Positive criteria for SAS		Total	*p* value*	Odds Ratio
		No	Yes			
Nocturnal HBP	**No**	22	2	24		
	Yes	20	6	26	0.25	3.3
Total		42	8	50		
Daytime HBP	**No**	30	2	32		
	Yes	12	6	18	0.019	7.5
Total		42	8	50		
Non-dipper profile	**No**	29	1	30		
	Yes	13	7	20	0.005	15.6
Total		42	8	50		

HBP: High blood pressure; SAS: Sleep apnea syndrome
* Fisher`s exact test

Table 6 - Blood Pressure levels between the various groups of oximetry

	Oximetry result			*p* value*
	Negative for SAS	Uncertain for SAS	Positive for SAS	
Mean systolic BP values [(± sd), mmHg]				
In office	143.4 (± 15)	149.5 (± 21.3)	161.6 (± 36)	0.084
In ABPM				
Day time	129.6 (± 10.9)	132.4 (± 12.2)	143.8 (± 20)	0.026
Night time	113.1 (± 14.5)	122.8 (±11.8)	136.8 (± 21.9)	< 0.001
Mean diastolic BP values [(± sd), mmHg]				
In office	78.9 (± 10.7)	78.6 (± 11.2)	79 (± 14.5)	0.997
In ABPM				
Day time	76.3 (± 9.1)	78.4 (± 10.2)	76.5 (± 7.7)	0.846
Night time	64.2 (± 9.2)	70.5 (± 8.6)	70.3 (± 5.5)	0.074
% of Dipping in MBP	13.3 (± 7.8)	8.5 (± 7.3)	5.8 (± 3.9)	0.022

ABPM: Ambulatory blood pressure monitoring; BP: Blood pressure; MBP: Mean blood pressure; SAS: Sleep apnea syndrome
* One-way ANOVA test

not easily diagnosed only through BP measurements in office, however this prevalence was lower than is the one reported by Konstantopoulou AS et al, 2006 (up to 42%).[15] Considering nocturnal HBP as an important marker of CVR,[9,10] a significant prevalence (52%) was found in our study.

SAS Prevalence

Comparing with other studies worldwide, with a prevalence ranging from 30 to 80%,[24,25] in this study the prevalence of SAS was low (16%). A low prevalence was also reported in 2014 in a Portuguese study performed by the DGS that found 1% in the general population; however the authors assumed that this value could be underestimated due to several reasons, highlighting the lack of adequate clinical records.[38] Despite the growing scientific evidence to sustain oximetry validity and utility,[27-31,39] it is not the reference exam (gold standard) for SAS diagnosis. In order to evaluate the oximetry results, we used a method with two different cutoff points, one representing 100% of sensitivity for the diagnosis and the other one representing 100% of specificity for the diagnosis exclusion. Therefore, between these two cutoff points there is an intermediate range of uncertain values which must be confirmed with PSG. For this reason, the obtained prevalence might be underestimated. In fact, beyond these eight positive cases

(with 100% sensitivity) other eight uncertain cases were obtained, these could increase the real prevalence up to 32% if they were confirmed as SAS, similarly to the reported bibliography.

Measuring BP in office and AMBP

A significant similarity between measuring BP in ABPM and measuring it in office was not found, and this means that these two methods are not equivalent (Table 4). Thus, ABPM has detected more 12% (six cases) of uncontrolled hypertensive patients compared to the office BP, suggesting that ABPM assessment is greater than the office evaluation regarding the diagnostic sensitivity, similar to what has been stated in several studies.[18-20] ABPM also provides valuable data for the CVR approach, such as blood pressure load[40] and pulse pressure,[41] and, also with some growing evidence, the variability of blood pressure[42] and the morning surge,[43] however this was not assessed in our study.

Association between SAS and uncontrolled HBP

A strong association was found between sleep apnea syndrome and uncontrolled daytime HBP, as well as between SAS and non-dipper profile (Tables 5), which supports the published literature.[12,13] Nevertheless, this association was not found with nocturnal HBP, which can be explained by the fact that almost half of the participants showing this profile have reported poor sleep quality during the examination and might be false positives. This phenomenon has been described by other authors,[44] but, although in this study it was not evaluated by the proper scales and tools, the participants might have been in light sleep or might had frequent awakenings, masking this association. Moreover, these cases may also represent false negative for SAS, being hidden by the failure to achieve a physiological deep sleep. By excluding these cases, the association between nocturnal HBP and SAS becomes statistically significant, similar to what was reported in the studies mentioned previously.

Beyond the eight positive cases of SAS detected by oximetry, other eight uncertain cases were obtained, as mentioned above. Among these additional cases, two had normal ABPM, but six had abnormal ABPM, predominating nocturnal HBP (n = 6) and non-dipper profile (n = 5). Furthermore, in a post-hoc analysis, the differences in systolic BP values and in % of nocturnal dipping between the various oximetry groups (Table 6) were only significant between the positive and the negative group. The uncertain cases of SAS showed, in almost every parameter, intermediate BP values between the negative and the positive groups. They can represent some mild form of SAS, not enough significant to be detected by oximetry, but serious enough to affect blood pressure control, once only two cases had ABPM values under the normal cutoff. This means that the lack of statistical significance in the association between sleep apnea syndrome and nocturnal HBP (Table 5) may actually exist and can become more evident if the uncertain cases of SAS are confirmed as sleep apnea syndrome. The small sample size, despite it is statistically representative of a larger target population, may also have compromised these results.

Limitations

Beyond the limitations already mentioned others should be remarked. Our study was not blind, since it design and methodology made it unenforceable, so it may exist an observer and participant bias. The prevalence of pure resistant hypertension was not evaluated by the ESH criteria, which, despite being low, may not be related to SAS. Although there is a strong association between SAS and uncontrolled HBP, there might be other causes of uncontrolled HBP that are not contemplated here.

Final remarks

This work reinforces the importance of ABPM in the control of high blood pressure and in the detection of different profiles which otherwise go undetected, such as nocturnal high blood pressure, masked HBP, white coat high blood pressure and the non-dipper profile. The results suggest that ABPM assessment is greater than the BP in office, and may have up to 12% more sensitivity. The prevalence of SAS is significant and this is related with uncontrolled HBP. Although SAS should be considered as a diagnostic hypothesis in the presence of suggestive clinical findings, the pulse oximetry can be an effective method for its detection and screening, and should be further explored and tested, with strong and well-designed studies with larger samples. The ABPM and pulse oximetry are complementary diagnostic methods, which should be considered simultaneously in a first HBP patient approach. These methods are in the scope of PHC and may be useful as appropriate tools for family doctors use in their clinical practice.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

FUNDING SOURCES

The authors declare and acknowledge the Portuguese Association of Family Medicine and General Practice© and the AstraZeneca© company for the support provided by funding this work within the context of "APMGF/AstraZeneca research grant 2013 - Primary Health Care". The received funding was an "unrestricted grant", which means that the sponsor had no influence either in the scientific methodology or the final contents of this work.

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