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# The influence of tobacco dependence on blood pressure control in people on antihypertensive drug treatment

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## KEYWORDS

Ambulatory blood pressure monitoring, smoking, community pharmacy

## ABBREVIATIONS

ABPM: Ambulatory blood pressure monitoring
BP: blood pressure
BPact: blood pressure during periods of activity
BPnoct: blood pressure at rest
CPh: community pharmacy
DBP: diastolic blood pressure
ESC: European Society of Cardiology
ESH: European Society of Hypertension
HTN: arterial hypertension
SBP: systolic blood pressure

## ABSTRACT

Smoking and hypertension are significant cardiovascular risk factors with a relationship that remains unclear.

*Objective:* To check for differences between smokers and non-smokers in blood pressure (BP) values obtained in a clinic, during activity, and at night, as well as white-coat hypertension, masked hypertension and the circadian profile.

*Patients and methods:* Consecutive opportunistic sampling of people on antihypertensive drug treatment who attended two community pharmacies between January 2013 and August 2019.

All of them underwent isolated measurement and ambulatory blood pressure monitoring (ABPM) for 24 hours.

*Results:* The sample consisted of 91 smokers and 573 non-smokers with an average age of 55.9 and 66.1 respectively, with males comprising 64.8% and 50.6%, respectively.

The following showed significant differences in the values between smoking and non-smoking patients: activity-related blood pressure (SBP/DBP): 132/80 mmHg smokers, 129/75 mmHg non-smokers. Masked uncontrolled hypertensive patients: 13.2% smokers, 12.0% non-smokers. Non-dipper profile: 34.0% smokers, 44.2% non-smokers.

*Conclusions:* Smokers had the highest blood pressure during periods of activity, and their higher prevalence of masked uncontrolled hypertension and dipper profile than non-smokers was statistically significant.

## INTRODUCTION

Cardiovascular disease is the leading cause of death and it is expected to remain so in the future. In 2015, 17.7 million people worldwide died from this disease (1), and 120,000 in Spain (2), which is respectively 30% and 28% of all deaths.

High blood pressure, smoking, diabetes, hypercholesterolemia, obesity, a sedentary lifestyle and heart rate disorders increase the risk of developing this type of disease. Of these vascular risk factors, high blood pressure and smoking are the most relevant (3).

Arterial hypertension is systolic blood pressure of at least 140 mmHg or diastolic blood pressure of at least 90 mmHg measured in a doctor's office (4). It affects 40% of the population (5) and is the direct cause of at least 51% of deaths due to cerebrovascular events and 45% of those with a cardiac origin (6).

Smoking is responsible for the deaths of 8 million people every year around the world (7). In Spain, tobacco causes at least 69,000 premature deaths per year. It not only increases the risk of cardiovascular diseases, but also of respiratory diseases and various types of cancer.

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The relationship between smoking and hypertension is unclear, though it is known that it causes an acute increase in blood pressure (8,9) and that they act in synergy to decrease left ventricular function (10). Some studies suggest that smokers have, in the medium and long term, lower blood pressure than non-smokers (11,12), while other publications (13,14) indicate the opposite.

Most published studies analyzing this association use clinical measurements (15,16) to determine blood pressure. Few have used ambulatory blood pressure monitoring (ABPM) even though it is the gold standard (17) for diagnosis of the disease because it provides 24-hour values, distinguishes between periods of activity (PAact) and periods of rest (PAnoct) and identifies phenotypes of hypertension such as white coat and masked.

Both pharmacies use ABPM in their daily clinical practice. If we add to this that the community pharmacist plays an important role as an active professional in stopping smoking, it means this study is important for obtaining data that relates both processes allowing us to classify the phenotype of the patients studied.

## AIMS

- To check for differences in clinically measured blood pressure between smoking and non-smoking patients with hypertension treated pharmacologically.
- To analyze the differences in blood pressure (BP) measured by ABPM during periods of activity (BPact), at night (BPNoct), and 24hour ambulatory blood pressure (24hrBP) in both patient groups.
- To study the prevalence of patients with uncontrolled white-coat hypertension and masked uncontrolled hypertension in subjects treated in the two groups cited.
- To examine the circadian profile of pharmacologically treated smoking and non-smoking patients with hypertension.

## MATERIALS AND METHODS

From January 2013 to August 2019, consecutive opportunistic sampling of people on antihypertensive treatment and systolic blood pressure under 180 and diastolic blood pressure under 110 mmHg was carried out in two rural Galician community pharmacies located in Celanova (Ourense) and Monfero (La Coruña). Anyone with an arm circumference greater than 42 cm, atrial fibrillation, arrhythmia, blood pressure monitor intolerance, comprehension limitations, people who did not want to participate in the study or who were insufficiently cooperative were excluded from the study.

In addition to recording age, sex and body mass index in the dominant arm (identified on the first day by taking readings from both arms) for each participant, three isolated blood pressure measurements were taken over four successive visits, using an OMRON M10-IT blood pressure monitor, calibrated, using a cuff appropriate to the arm circumference and following the recommendations of the European Society of Cardiology and the European Society of Hypertension (ESC/ESH) guidance on the diagnosis and treatment of arterial hypertension (4) including 5-minute rest as well as abstinence from smoking, alcohol, caffeine, and exercise in the 30 minutes prior to the blood pressure measurement. Each of these four measurements was the average of three separate readings taken one minute apart.

After a few days, each participant carried an ABPM for 24 hours with a Watchbp03 monitor, which took readings every 20 minutes during periods of activity and every 30 minutes during rest. All subjects recorded the times they went to bed and got up, their physical activity, and medication time in a diary. ABPM tests that met the following criteria were considered valid (18):

- Records valid for 24 hours >70%.
- 20 valid readings in the period of activity.
- 7 valid readings in the period of rest.
- ≥2 valid readings/hr during the period of activity and 1 valid reading/hr during sleep.

The threshold values (4) for the clinical readings and ABPM periods are defined in table 1.

**Table 1** Definitions of hypertension according to office and ambulatory blood pressure figures

| Category | SBP (mmHg) | DBP (mmHg) |
|---|---|---|
| Office BP | ≥ 140 | ≥ 90 |
| Ambulatory BP | | |
| Diurnal | ≥ 135 | ≥ 85 |
| Nocturnal | ≥ 120 | ≥ 70 |
| 24 hr average | ≥ 130 | ≥ 80 |

SBP: systolic blood pressure; DBP: diastolic blood pressure; BP: blood pressure.

Adapted from: Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018 Sep 1;39(33):3021-3104.

Using ABPM to take blood pressure readings enabled us to obtain phenotype information from the patients studied and to classify the (19) participants.

We defined any participant who met the following conditions as a patient with uncontrolled hypertension: arterial pressure at rest ≥140/90 mmHg for clinical readings and mean arterial pressure for periods of activity ≥135/85 mmHg or mean nocturnal arterial pressure ≥120/70 mmHg or mean arterial pressure in 24 hours ≥130/80 mmHg for ABPM (table 2).

A patient was considered controlled if all their clinical readings and all ABPM periods were below the above-mentioned values (table 2).

A patient was defined as having uncontrolled white coat hypertension if they met all the following conditions: arterial pressure ≥140/90 mmHg in clinical readings and mean arterial pressure during periods of activity <135/85 mmHg and mean nocturnal arterial pressure <120/70 mmHg and 24-hour mean arterial pressure <130/80 mmHg for ABMP (table 2).

A patient was defined as having uncontrolled white coat hypertension if they met all the following conditions: blood pressure <140/90 mmHg in clinical readings and mean arterial pressure in periods of activity ≥135/85 mmHg and mean nocturnal arterial pressure ≥120/70 mmHg and 24-hour mean arterial pressure ≥130/80 mmHg for ABMP (table 2).

**Table 2** Hypertension phenotype determined from office and ambulatory BP readings in treated persons

| People in treatment | Normal office BP <140/90 | Pathologic office BP ≥140/90 |
|---|---|---|
| Normal ABPM <130/80 24 hr and <135/85 diurnal and <120/70 nocturnal | Controlled HTN | Uncontrolled white coat HTN |
| Pathologic ABPM ≥130/80 24 hr and/or ≥135/85 diurnal and/or ≥120/70 nocturnal | Masked controlled hypertensive patients | Uncontrolled HTN |

BP: blood pressure; HTN: Arterial hypertension; ABPM: Ambulatory blood pressure monitoring.

Table adapted from: T. Gijón-Conde, M. Gorostidi, J.R. Banegas, A. de la Sierra, J. Segura et al. Document of the Spanish Society of Hypertension-Spanish League for Combating Hypertension (SEH-LELHA) on ambulatory blood pressure monitoring (ABPM) 2019. Vasc Risk Hyperten. 2019; 36(4):100-212.

Depending on the reduction (4) between the mean nocturnal BP readings in relation to average daytime BP, participants were classified as:

- Dipper: Any participant who experienced a nighttime drop in systolic blood pressure greater than 10% of their average daytime blood pressure.
- Extreme dipper: Any participant who experienced a nighttime drop in systolic blood pressure higher than 20% of their average daytime blood pressure.
- Non-dipper: Any participant whose nighttime drop in blood pressure was less than 10% of the average of his or her daytime blood pressure.
- Riser: Any participant whose mean nighttime blood pressure was not lower than their daytime blood pressure.

The presence of antidiabetic drug treatment or a diagnosis of it helped us assess whether the patient had diabetes.

For the purposes of this study, any subject who currently smokes and who has smoked tobacco or other forms in the past six months was considered a smoker. All patients underwent at least one brief intervention.

All patients signed an informed consent to participate in the study in compliance with the Data Protection Act (LOPD).

Quantitative variables were compared using the Student t test. Qualitative variables were compared using Pearson's chi-squared test. Differences with an alpha probability of error with $p < 0.05$ were considered statistically significant. The data are expressed as mean ± standard deviation.

SPSS® version 24 was used for statistical analysis of the data.

## RESULTS

In the period mentioned, approximately 4,000 people with antihypertensive treatment passed through the pharmacies in which the study was conducted, of which 794 agreed to participate. Of these, 73 were excluded having met one or more of the above criteria. Of the remaining 721 participants, nine were eliminated due to removal of the blood pressure tester before 24 hours and forty-eight for not having obtained a sufficient percentage of valid readings during the 24 hour period.

The final sample was therefore made up of 664 persons (52% males), aged 64 ± 10 years and body mass index 30 ± 4 kg/m$^2$.

Table 3 shows the mean and standard deviation of the parameters measured disaggregated patient group and table 4 displays the interpretation of these values.

**Table 3** Comparative summary between smoking and non-smoking patients

| | Smokers N=91 | Non-smokers N=573 | |
|---|---|---|---|
| | % | % | p value |
| Males (%) | 64.8 | 50.6 | |
| Diabetes (%) | 13.2 | 24.8 | 0.001 |
| | Mean ± standard deviation | Mean ± standard deviation | |
| Age (years) | 55.9 (10.4) | 66.1 (10.3) | |
| BMI (kg/m$^2$) | 28.4 (5.2) | 30.7 (4.5) | |
| No. of active ingredients used for BP | 1.6 (0.9) | 1.9 (1) | |
| Isolated SBP (mmHg) | 144 (19) | 145 (20) | 0.47 |
| Isolated DBP (mmHg) | 88 (11) | 85 (11) | 0.02 |
| HR (bpm) isolated reading | 77 (12) | 71 (11) | 0.05 |
| 24 hr ABPM SBP (mmHg) | 128 (15) | 126 (13) | 0.04 |
| ABPM SBP in activity (mmHg) | 132 (15) | 129 (13) | 0.03 |
| SBP ABPM at rest (mmHg) | 118 (17) | 118 (15) | 0.8 |
| 24 hr DBP ABPM (mmHg) | 77 (8) | 72 (9) | 0.003 |
| DBP ABPM in activity (mmHg) | 80 (9) | 75 (9) | 0.01 |
| DBP ABPM at rest (mmHg) | 68 (9) | 66 (9) | 0.01 |

Mean values and standard deviation of measured parameters disaggregated by patient group.
BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate; ABPM: Ambulatory blood pressure monitoring; SD: Standard deviation.

**Table 4** Comparison of phenotypes and circadian profile between the two patient groups

| | Smokers | Non-smokers | p value |
|---|---|---|---|
| Degree of control with clinical reading and ABPM (%) | 17.6 | 24.3 | 0.00 |
| Uncontrolled white-gown hypertensive patients in treated subjects (%) | 18.7 | 21.4 | 0.00 |
| Masked uncontrolled hypertensive patients in treated subjects (%) | 13.2 | 12 | 0.00 |
| Dipper (%) | 51.6 | 36.5 | 0.00 |
| Non-dipper (%) | 34.1 | 44.2 | 0.00 |
| Extreme dipper (%) | 6.6 | 5.3 | 0.00 |
| Riser (%) | 7.7 | 14 | 0.00 |

ABPM: Ambulatory blood pressure monitoring.

The age and body mass index of the non-smoking group were significantly higher than those of the smoking group. The percentage of patients with diabetes was higher in non-smokers. The number of antihypertensive drugs in both groups was not significantly different.

## DISCUSSION

The nicotine contained in cigarettes stimulates the adrenal medulla by releasing catecholamines, which increases heart rate, cardiac output and blood pressure among other things, but, according to our results, this effect appears to be short lived.

Epidemiological studies have evaluated casual office blood pressure readings of smokers and found that the results were the same, or even lower, than for the non-smokers (20,21). These results coincide with those obtained in our study. Clinically, systolic blood pressure levels are slightly lower for smokers (144 mmHg) when compared with non-smokers (145 mmHg) p=0.047. This may be because in performing clinical BP measurements the patient should not

have smoked, drunk caffeinated drinks, or exercised, etc., in the 30 minutes before taking the reading, as stated in the ESC/ESH 2018 Guidelines on the diagnosis and treatment of arterial hypertension (4).

However, in the values obtained by ABPM, we observed that the SBP/DBP readings during periods of activity were higher in the smokers (132 vs. 129 mmHg) (p=0.03). These results are consistent with those obtained in previous publications (22,23), though populations of similar ages were studied in these publications. In this case the hypertensive effect of tobacco may have been recorded, as the BP readings could have been taken within 30 minutes of the patient smoking their last cigarette. This may suggest that tobacco use may reduce the likelihood of pharmacological control of hypertension. The mean systolic blood pressure values at rest are practically the same (118 vs. 118) (p=0.8). We found consistency with the same studies (22,23). The most likely cause may be that during rest periods, patients do not usually smoke.

We have found other studies (24,25) with results that are consistent with ours, but in these cases the participants were normotensive.

Regarding the phenotype studied: in smokers we found a higher percentage of masked uncontrolled hypertensive patients in treated subjects, the same as in previous studies (26,27). Smoking, alcohol consumption, physical activity, and psychosocial factors (anxiety, interpersonal conflict, and work stress) can contribute to increasing the ambulatory blood pressure monitoring readings (28). Patients with masked hypertension have poor out-of-office control of blood pressure and this type of clinical condition leads to an increased risk of cardiovascular events (29,30), higher cardiovascular mortality and stroke (31). This is because in reality the patient's blood pressure is not actually controlled (they only have good control in office). These patients need to increase their antihypertensive treatment and stop smoking to improve control and thereby decrease cardiovascular mortality and stroke.

Uncontrolled white coat hypertension in treated subjects is usually more related to age and sex. In our study it applies more to the non-smoking group, like in the studies by Stanley S. et al. (32) and Green et al. (33). Those studies show that the relationship between age and diabetes is a key factor in white coat hypertension. In our study, non-smoking patients, with a higher percentage of white coat hypertension, are older than the group of smokers.

Exposure to cigarette tobacco smoke has been shown to cause specific alterations in heart rate variability parameters due to the predominance of friendly parameters in cardiac autonomic tone. In our study, as in others (34,35), heart rate readings were higher in the group of smokers than the non-smokers (p=0.05).

Regarding the circadian profile we found a higher percentage of patients with a dipper profile (52 vs. 36; p<0.05; **table 4**) in smoking patients, due to the higher difference in readings between periods of activity and periods of rest. In non-smoking patients, having lower SBP levels during periods of activity and equal nocturnal BP levels makes the percentage of non-dipper patients the predominant profile.

Numerous studies (36,37) show that patients with dipper patterns have a better prognosis, as they have fewer cardiovascular and cerebrovascular events, as well as lower mortality.

A significant limitation is that our sample is likely not representative of the general population, nor of the hypertensive population, as there are patients with treated hypertension who visit two pharmacies and how they select which one is a source of bias that limits the conclusions (38).

Other circumstances in our study that could bias the results. We believe that the difference in size between groups (38) (the sample of smokers is one-sixth of that of non-smokers), the significant difference in body mass index, sex, or diabetic patients in both groups can be biased when comparing results.

We can deduce that smokers who are 10 years younger are "healthier" in general. In non-smokers 24% of patients have diabetes; this can also affect the circadian pattern because this group of patients usually has a non-dipper circadian profile (39).

It is significant that the sample from our study was from the general population and of varying ages (28 to 92 years) taken through a proactive approach by a community pharmacist offering ambulatory pressure monitoring to all patients in the study. While random sampling would likely have had its advantages, the consecutive sampling allowed us to obtain a considerable size sample.

## CONCLUSIONS

- We found no significant differences between the two groups in our sample in terms of systolic blood pressure as a clinical reading.
- There were significant differences in blood pressure during the period of activity obtained from ambulatory blood pressure monitoring.
- Pharmacologically treated smokers with hypertension had significantly higher levels of masked uncontrolled hypertension.
- The non-dipper profile was predominant in the group of non-smoking patients treated for hypertension.

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