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Diagnostic and therapeutic phenotypes in patients with high blood pressure

Fenotipos diagnósticos y terapéuticos en pacientes con hipertensión arterial

Héctor Galván-Oseguera, MD,* Agustina Moreno-González, MD‡

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ABSTRACT

In patients with high blood pressure (HBP), we can find different characteristics which can help us establish the diagnosis, prognosis, and treatment. With the advancement of technology and knowledge of the pathophysiology of HBP, we now have other diagnostic methods outside the office which allow us to measure BP in different circumstances. Within HBP individual patients may have disease attributes that, alone or in combination, describe different phenotypes between individuals in relation to parameters which have clinical significance. Some of the main characteristics that we identify are those related to BP measurement, to the origin of BP elevation, to the circumstance in which BP was taken, to patients with high BP variability, patients who do not respond to treatment, patients where elevation of their BP is an emergency and one of the most important according to cardiovascular risk. From these characteristics we were able to identify 29 different HBP phenotypes in the literature, which can help us better define diagnosis, prognosis, and treatment. Many authors and clinicians call it a "tailor-made suit"; however, we will call it the hypertensive phenotype.

RESUMEN

En los pacientes con hipertensión arterial (HTA) podemos encontrar diferentes características que nos pueden ayudar a establecer el diagnóstico, el pronóstico y el tratamiento. Con el avance de la tecnología y el conocimiento de la fisiopatología de la HTA, ahora disponemos de otros métodos de diagnóstico fuera de la consulta que nos permiten medir la PA en diferentes circunstancias. Dentro de la HTA, los pacientes individuales pueden tener atributos de la enfermedad que, solos o combinados, describen fenotipos diferentes entre los individuos en relación con parámetros que tienen importancia clínica. Algunas de las principales características que identificamos son las relacionadas con la medición de la PA, con el origen de la elevación de la PA, con la circunstancia en la que se tomó la PA, con los pacientes con alta variabilidad de la PA, con los pacientes que no responden al tratamiento, con los pacientes en los que la elevación de su PA es una urgencia y con uno de los más importantes según el riesgo cardiovascular. A partir de estas características pudimos identificar 29 fenotipos diferentes de HTA en la literatura, que pueden ayudarnos a definir mejor el diagnóstico, el pronóstico y el tratamiento. Muchos autores y clínicos lo llaman «traje a medida»; sin embargo, nosotros lo llamaremos fenotipo hipertensivo.

* Head of the Adult Degenerative and Congenital Valvular Cardiopathy, Member of GREHTA.
‡ Clinical cardiologist at the Adult Degenerative and Congenital Valvular Cardiopathy, Member of GREHTA.

Department at the Cardiology Hospital of Centro Médico Nacional Siglo XXI del Instituto Mexicano del Seguro Social.

INTRODUCTION

High blood pressure (HBP) is the main risk factor for mortality world-wide. In Mexico its prevalence reaches over 34% in adults over 20 years of age.[1,2] Being such an important and prevalent disease, it requires consistent methods for its diagnosis. This diagnosis is mainly based on taking blood pressure (BP) using a cuff to compress the upper arm, a technique that is still valid to this day and has not changed in more than 100 years. With the advancement of technology and knowledge of the pathophysiology of HBP, we now have other diagnostic methods outside the office which allow us to measure BP in different circumstances.[3]

Arterial BP is related to intrinsic biological rhythms of a periodic nature, generally 24 hours, called the circadian cycle. This circadian cycle shows that BP is a biological parameter

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with great variability, which can be observed beat by beat or minute by minute (short-term), day by day and visit by visit (medium-term) and year by year (long-term variability). There are many factors that influence this variability, such as the daily duration of sunlight, which in turn depends on the seasons of the year, day of the week, influenced by the work rhythm and the duration of rest or effort, sleeping, or eating schedule, exercise, including the place, time, and position in which the BP is taken, among other variables. In addition to these external factors, there are also factors specific to the individual, such as their genotype, age, gender, or body complexion, which make each BP intake different for each person.[4]

High blood pressure is a massive phenomenon; however, each patient may have attributes of the disease that, alone or in combination, describe differences between individuals in relation to parameters that have clinical significance. Many authors and clinicians call it a «tailor-made suit»; however, we will call it a hypertensive phenotype *(Figure 1)*.

Classification of patients with high blood pressure and its phenotypes

According to the Official Mexican Standard NOM-030-SSA2-2009, HBP in adults is classified according to the degree of BP elevation measured in mmHg taken in the office.[5] This classification is consistent with most of the Clinical Practice Guidelines in the world mainly from the WHO, Latin America, and Europe.[6-8] In recent years, with the advent of diagnostic methods outside the office, such as Ambulatory Blood Pressure Monitoring (ABPM) and Home Blood Pressure Monitoring (HBPM), other parameters measured in averages were added to the definition, these definitions are already the NOM-030-SSA2-2017 project and have been adopted in Mexico[9] *(Table 1)*.

Although these definitions prevail to make the diagnosis and make the corresponding therapeutic decisions, there is a set of different characteristics that each hypertensive patient presents because of the interaction between their genotype and the environment in which they live, which is known as phenotype. In the case of patients with AHT, we will see below the different phenotypes with their corresponding characteristics.

1. Phenotypes according to BP measurement

These phenotypes are generally found when making the diagnosis in the office:

1. Patients with isolated diastolic HBP
2. Patients with isolated systolic HBP
3. Patients with systolic-diastolic HBP

Although there are some differences in the cut-off points for the definition of HBP, mainly with the most recent guide published by the American Heart Association/American College of Cardiology (AHA/ACC) and the guidelines recently published by the International Society Hypertension (ISH),[10] in Mexico we use the one that resembles the European guide in accordance with NOM 00308.[5] Its identification can help us define both the pathophysiology and treatment, since some patients with isolated diastolic HBP respond better to the use of BB, while those with isolated systolic and systolo-diastolic HBP respond better to the use of combinations based on angiotensin inhibitors. angiotensin converting enzyme (ACE)/angiotensin 2 receptor antagonists (ARA 2), Calcium antagonists or thiazide-type diuretics.

2. Phenotypes according to origin

There are also phenotypes according to the origin or cause of HBP, in which «primary or essential» is the most prevalent, followed by secondary (where there are many phenotypes) and pregnancy related. These phenotypes are the most used in the clinic; we know that the origin of more than 95% of patients with HBP is unknown, what we call primary or «essential» HBP, although it is known that its etiology is multifactorial. Another important phenotype is related to secondary causes that we mainly find in children, young patients, or patients whose BP control is very difficult.

Finally, HBP during pregnancy, which is the main cause of maternal death in Mexico, so its identification is very important. Here we can find 3 different phenotypes:

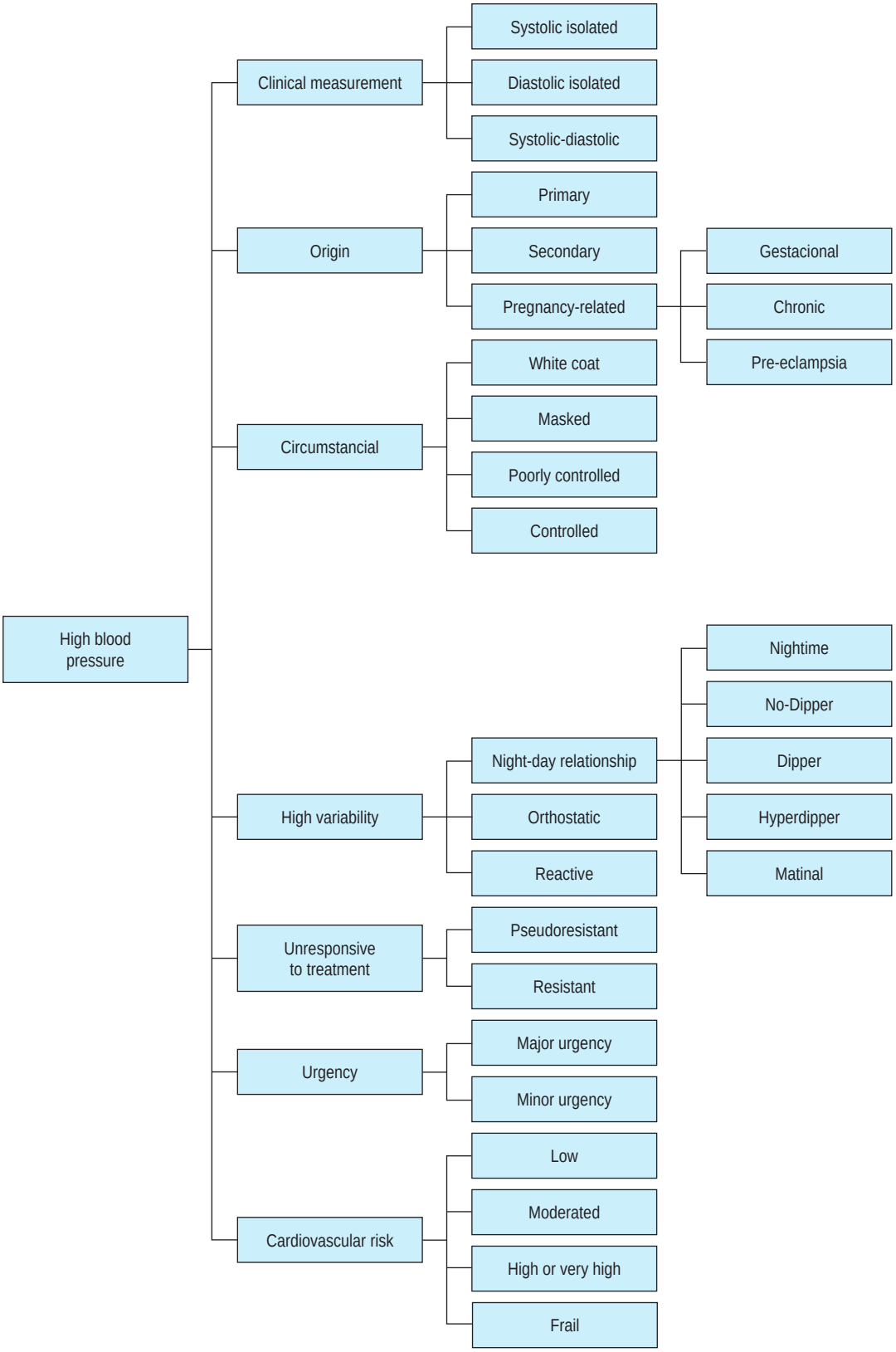

Figure 1:

High blood pressure phenotypes. Classification proposed by Dr. Héctor Galván Oseguera and Dra. Agustina Moreno González.

1. **Gestational HBP:** this is HBP that develops during pregnancy. It begins after 20 weeks of pregnancy.
2. **Chronic HBP in pregnancy:** this is high BP that begins before the 20th week of pregnancy or before becoming pregnant.
3. **Preeclampsia:** it is a sudden increase in blood pressure after the 20th week of pregnancy. In general, it occurs in the last trimester and can continue in the postpartum period.

Table 1: Definiton of high blood pressure based on BP measurement

Modality	Systolic BP mmHg	Diastolic BP mmHg
In office	≥ 140	≥ 90
Out-of-office		
Daytime (vigil)	≥ 135	≥ 85
Nightime (sleep)	≥ 120	≥ 70
24-hour average	≥ 130	≥ 80
Home-based	≥ 135	≥ 85

BP = blood pressure.
Source: 2018 ESC/ESH guidelines for the diagnosis and treatment of high blood pressure.[7]

The characteristics of these phenotypes can be seen in *Table 2*.

3. Circumstancial high blood pressure phenotypes

Other phenotypes are those given by diagnostic methods outside the office such as ambulatory blood pressure measurement (ABPM) and home blood pressure monitoring (HBPM) called «circumstantial» HBP, which includes 4 other phenotypes such as white coat HBP, masked HBP, sustained or uncontrolled HBP and controlled HBP or normotension *(Table 3)*. This differentiation depends on the place and time in which the blood pressure measurement is done, the so-called «white coat» HBP is characterized when the patient has high BP in office measurements and normal outside the office, while in "masked" HBP the opposite happens: BP inside the office is normal, while intake outside the office is high, when BP is high both in office and outside the office, we are dealing with a patient with sustained or uncontrolled HBP. This is also the case of patients with normal BP inside and outside the office, which allows us to rule out the diagnosis

Table 2: High blood pressure phenotypes according to clinical measurements.

Phenotype	Isolated diastolic high blood pressure	Isolated systolic high blood pressure	Systolic-diastolic high blood pressure
Definition	ESH: DBP > 90 mmHg, SBP < 140 mmHg AHA/ACC: DBP > 80 mmHg, SBP < 130 mmHg NOM 0030: DBP > 90 mmHg, SBP < 140 mmHg	ESH: DBP < 90 mmHg, SBP > 140 mmHg AHA/ACC: DBP < 80mmHg, SBP > 130 mmHg NOM 0030: DBP < 90 mmHg, SBP > 140 mmHg	ESH: DBP > 90 mmHg, SBP > 140 mmHg AHA/ACC: DBP > 80 mmHg, SBP > 130 mmHg NOM 0030: DBP > 90 mmHg, SBP > 140 mmHg
Etiology	Multifactorial, mainly in young adults	Multifactorial, mainly in older adults	Multifactorial, mainly in adults > 40 years
Pathophysiology	Mainly by increases in sympathetic and heart output activity	Mainly by increases in arterial stiffness	Mainly by increases in vascular resistance
Prognosis	Long-term morbidity and mortality	High mortality and morbidity	High mortality and morbidity
Treatment	ACEI/ARB and in some patients BB	Combinations of ACEI/ARB, calcium channel blockers and thiazide diuretics	Combinations of ACEI/ARB, calcium channel blockers and thiazide diuretics

ESH = European Society high blood pressure; ACEI = Angiotensin-converting enzyme inhibitors; ARB = Angiotensin receptor blockers; BB = Beta-blockers.

Table 3: High blood pressure phenotypes according to origin or cause .

Phenotype	Primary or essential	Secondary	Pregnancy-related
Definition	Permanent elevation of systolic and/or diastolic BP without defined cause	Permanent elevation of systolic and/or diastolic BP with a defined cause. It is suspected when it begins in childhood or young patients, or patients with refractory or resistant high blood pressure.	Gestational high blood pressure: Elevated blood pressure during pregnancy. It begins after 20 weeks of pregnancy. Chronic high blood pressure in pregnancy: High blood pressure that begins before the 20th week of pregnancy or before becoming pregnant. Preeclampsia: Sudden increase in blood pressure after the 20th week of pregnancy. In general, it occurs in the last trimester and can continue in the postpartum period.
Etiology	Multifactorial: genetic, cultural and environmental causes.	Frequent: Primary hyperaldosteronism, renal parenchymal diseases and renal artery stenosis. Rare: Aortic coarctation, Pheochromocytoma, Cushing's syndrome, Hyperparathyroidism, Brain tumors, Takayasu's disease and other vasculitides, etc.	Unknown
Pathophysiology	Mainly due to increased vascular resistance and cardiac output	Depends on the cause	Generalized inflammation, prothrombosis and proteinuria.
Prognosis	High mortality and morbidity.	Variable	Premature birth, fetal and maternal death.
Treatment	ACEI/ARB combinations, calcium antagonists and thiazide-type diuretics are preferred.	Depends on the cause	Acetyl-salicylic acid, Calcium antagonists, alpha-blockers and beta-blockers.

ESH = European Society high blood pressure; ACEI = Angiotensin-converting enzyme inhibitors; ARB = Angiotensin receptor blockers; BB = Beta-blockers.

or to know that the hypertensive patient is well controlled. We will delve deeper into these phenotypes due to their clinical importance.

White coat high blood pressure (or isolated clinical high blood pressure)

White coat HBP (WCHBP) is an important phenotype as it is a proposed risk factor for the development of sustained HBP, target organ damage, and possibly the occurrence of cardiovascular (CV) events. Recently, interest in this phenotype has increased since, some studies have identified that WCHBP increases the relative risk of sustained HBP, almost three times compared to patients with normal BP, as well as the risk of carotid atherosclerosis and impaired cardiac function. Current evidence suggests that WCHBP is an intermediate risk category located somewhere between those with normotension and sustained HBP.[11] This contrasts with other studies, which have found that patients with WCHBP have no additional CV risk; this apparent lack of clarity

deserves further investigation.[12,13] Evidence based on randomized controlled trials is scarce and the results of existing studies are controversial so far on WCHBP. The white coat effect is not necessarily the same as the alert reaction produced by the presence of health personnel when taking BP, since other factors can contribute to the white coat effect, such as patient anxiety.[14,15] This effect can be reduced with a correct and repeated measurement of BP in consultation, it is usually lower in nursing consultations and tends to disappear with non-face-to-face clinical measurement.[16]

Prevalence: the prevalence of WCHBP varies according to the studies because its definition has been based both on mean daytime blood pressure cut-off points and 24-hour blood pressure values. Based on cut-off points of 140/90 mmHg for normal office BP and 135/85 mmHg for normal daytime BP, the prevalence of white coat HBP ranges from 20 to 45%.[17] Regarding the factors that predispose to the development of the WCHBP phenotype, non-smokers, women over 55 years of age, obese and with higher clinical systolic blood pressures (mild HBP) are more likely to develop white coat HBP.[18]

Etiology and pathophysiology: there are several proposed triggers for the development of WCHBP. Patients have a slight elevation in BP on arrival at the consultation and during manual recordings of BP with a cuff and manometer, these elevations in BP exceed those recorded by ABPM during the episodes of anxiety or aggravation. Psychological characteristics, particularly anxiety, could be responsible for the presence of WCHBP. Anxiety is an emerging risk factor for CV disease, but its role in WCHBP is less clear. In patients treated with antihypertensives, high levels of anxiety have been shown to increase the risk of pseudo resistant HBP due to the white coat effect. These findings contrast with previous work showing that psychological characteristics do not differ between those with WCHBP and sustained HBP.

A hypothesis has been described which involves the sympathetic and endocrine systems as being involved in the genesis of WCHBP. This has been investigated by simultaneously measuring arterial BP, heart rate, and sympathetic nerve activity in the skin and postganglionic muscles during a visit to the doctor, where subjects showed elevation in both BP and heart rate during the visit. This was accompanied by an increase in skin sympathetic nerve stimulation and a corresponding reduction in muscle sympathetic nerve stimulation. Except for sympathetic nerve stimulation of the skin, these changes persisted for several minutes after the visit ended. A nurse visit elicited a significantly attenuated response compared to a physician visit. The endocrine system may play an important role in BP recovery in the hours rather than minutes after a clinic visit. Hospital-initiated ABPM shows that it takes 2 to 3 hours for BP to reach usual daytime values. This could be explained by a prolonged sympathetic response or by some endocrine contribution.[5]

Cardiovascular risk: WCHBP is well characterized in the medical literature, but there is still no consensus on its prognostic importance in cardiovascular disease (CVD). However, growing evidence has begun to establish a link between WCHBP and risk factors associated with CVD, namely the development of Sustained HBP (SH) and the presence of target organ damage. Both are important and independent predictors of CV risk. Some patients with WCHBP may have an increased cardiovascular risk due to concomitant risk factors (smoking, dyslipidemia, diabetes, metabolic syndrome) or the presence of target organ damage or associated cardiovascular disease. There are doubts about the long-term prognosis, but there is sufficient evidence to show that cases with WCHBP have lower cardiovascular morbidity and mortality than sustained hypertensives and masked hypertensives, although higher than normotensives. Therefore, their cardiovascular risk would be intermediate between normotension and sustained HBP. Regarding the prevalence of target organ damage, most studies conclude that WCHBP presents greater subclinical organ involvement than normotension.[19]

Treatment: the need for pharmacological treatment is the most controversial point in the management of these patients. If we consider that subjects with WCHBP would

have a better prognosis than hypertensive, but worse than normotensive individuals, it might not be essential to prescribe antihypertensive treatment, unless there is evidence of organ involvement. Antihypertensive drugs have been shown to reduce clinical blood pressure more than ambulatory blood pressure in these patients, and there is little evidence of the potential benefit of pharmacological treatment. However, the decision to start antihypertensive drugs must be individualized and will depend on concomitant risk factors, the presence of subclinical organ damage, as well as associated cardiovascular diseases.[20]

In the HALT (Hypertension and Lipid Trial) study, Pickering et al. reported that administration of doxazosin, a long-acting alpha-1-blocker, lowered BP in patients with sustained HBP but not in those with WCHBP; however, it was equally effective on clinical blood pressure maintenance in both groups. Other investigators have reported similar results using different calcium channel blockers. On the other hand, Herpin et al. found that calcium channel blockers were ineffective in lowering ambulatory blood pressure (ABP) in patients with WCHBP, whereas angiotensin-converting enzyme (ACE) inhibitors were effective. However, both classes of drugs were effective in lowering clinical blood pressure. Similar results were reported by Kristensen et al. using felodipine (a dihydropyridine-type calcium channel blocker) and benazepril (an ACE inhibitor). In patients with WCHBP, benazepril was more effective in lowering BP. These studies suggest that the efficacy of various antihypertensive drugs in lowering BP in patients with WCHBP may differ. However, resistance to drug effect is most likely due to ABP level because patients with low-normal ABP were more resistant to treatment. This was confirmed by the studies by Fagard et al.; these authors used lisinopril and isradipine to treat HBP and found a daytime resistance PAA of 128/88 mmHg. Given the studies showing resistance to pharmacological treatment in patients with WCHBP and the results of the recent Hypertension Optimal Treatment (HOT) study showing no cardiovascular benefit in reducing blood pressure below 138.5/86.5 mmHg, except in diabetic patients, drug treatment of WCHBP should be discontinued. Instead, a nonpharmacologic management approach should be instituted.

From the outset, early intervention should be carried out on the patient's other cardiovascular risk factors. In addition, all patients with WCHBP should be treated with an intensive and comprehensive lifestyle improvement intervention. The non-pharmacological approach should include the following: modification of the patient's lifestyle, moderate salt restriction, weight loss if the patient is obese, regular exercise, smoking cessation, moderation of alcohol consumption, correction of abnormalities of blood glucose and lipids and regular follow-up for control every 6 or 12 months. By doing so, those patients who will develop sustained HBP could be detected early.

The European Society of Hypertension (ESH) has developed guidelines for the treatment of WCHBP. They suggest that patients with WCHBP and no additional CV risk factors should be managed with lifestyle changes and closely followed due to their increased risk of developing cardiovascular complications. In individuals with WCHBP and evidence of HBP-mediated organ damage or elevated CV risk, it may be appropriate to offer recommendations for lifestyle changes in conjunction with pharmacological treatment *(Figure 2)*.

Masked high blood pressure

Definition: Masked HBP (MHBP) describes a situation that occurs when clinic BP in individuals without antihypertensive treatment is < 140/90 mmHg and ambulatory BP is above reference values (130/80 mmHg in 24 h, 135/85 mmHg during daytime, or 120/70 mmHg during nighttime). In 2002, Pickering coined the term MH; MH or masked uncontrolled HBP is defined as a person who has normal blood pressure in the office and hypertensive blood pressure outside the office. The term MHBP is reserved for treatment-naïve patients and uncontrolled HBP for patients with treated HBP. Although recent emphasis on out-of-office BP measurement has led to increased recognition of the masked phenomenon, there is a lack of awareness of this phenomenon among clinicians. Furthermore, many aspects of this phenomenon remain unclear.[21]

Classification: MH can also be classified according to ABPM into two types:

1. Masked daytime HBP: this pattern is seen in people with job stress, smoking, poor exercise tolerance, or excessive alcohol use.
2. Masked nocturnal HBP: this is seen in the context of obstructive sleep apnea (OSA), diabetes, chronic kidney disease (CKD), sleep deprivation, or metabolic disorders.[22]

Prevalence: Current data on the prevalence of MH are highly variable due to differences in the ethnic origin of the study groups, the heterogeneous definition of MH, and the measurement tools used (ABPM/Daytime/Nighttime ABPM/24-hour ABPM) for its measurement diagnosis. In general, the prevalence of MH in the general population ranges between 8.5 and 16.6%. The prevalence increased to 30.4% in populations with high normal clinical BP. In a systematic review by Thakkar et.al, the prevalence of MH was significantly higher in patients of African ethnicity with a prevalence of up to 52.5% in African Americans compared to lower values in Korean patients (5.7%). and Omanis (6.0%) offspring. The presence of comorbidities also influenced the prevalence of MH, with 30% in OSA, 13.3 to 66.4% in diabetes, 7 to 32.8% in CKD, 15% on hemodialysis and 16 to 39% in kidney transplant recipients.[21]

Etiology and pathophysiology: Mechanisms which lead to MH can be classified into two groups that may not be mutually exclusive:

1. **Low office BP relative to ambulatory BP.** The exact cause of low office BP relative to ambulatory BP is unknown. But extrapolating from our understanding that WCHBP may be in part a conditioned anxiety response that is relatively specific to the clinical setting, the reverse might be true in MH, where the anxiety or stress response is greater outside of the doctor's office. Office BP in some elderly hypertensives measured after meals may show a significant postprandial reduction leading to a diagnosis of MH.
2. **Selectively high ambulatory BP.** Lifestyle factors such as smoking, alcohol, physical inactivity, interpersonal relationships. mental anxiety and work stress could selectively increase ambulatory BP. Sedentary and obese individuals may have poor exercise tolerance through daily activity and show prehypertensive office BP values when measured at rest. Exaggerated BP response to exercise (EBPRE) is also associated with MH. Kayrak et al studied sixty-one

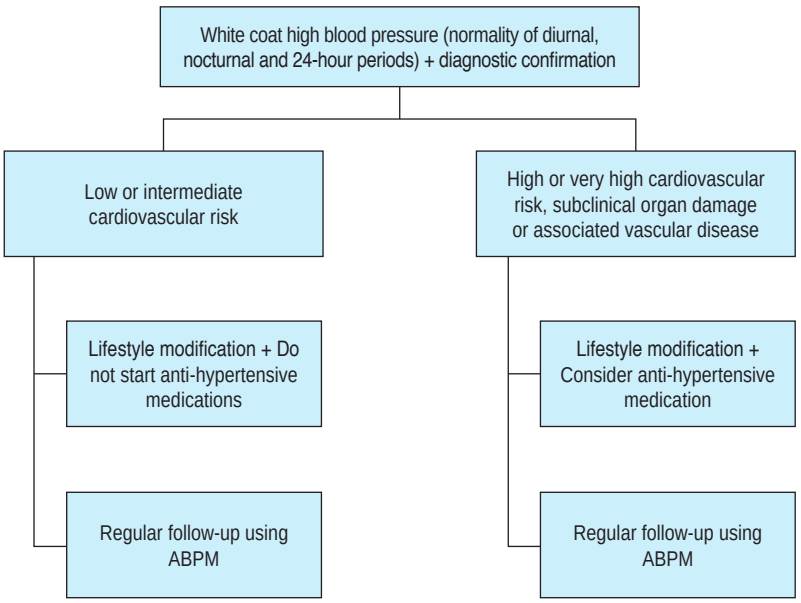

Figure 2:

Management of White coat high blood pressure. Source: Vinyoles et al, 2020.

normotensive patients with EBPRE by ABPM. The prevalence of MH in subjects with EBPRE was 41%. Diastolic BP measured at maximal exercise was an independent predictor of MH in EBPRE. Because of these factors, BP measurement should be based on anxiety-neutral approaches, such as automated office blood pressure (AOBP) and ABPM or LMWH outside the office.

Therefore, MH is higher in subjects with normal-high BP and being male, young age, being a smoker and drinker, a high level of physical activity, anxiety and work stress are predictive factors. Family history of HBP and associated CVD risk factors, such as diabetes, hypercholesterolemia, the presence of organ damage, and chronic kidney disease, are associated with a higher risk of masked HBP. Exercise-induced HBP also increases the probability of MH. Sleep apnea hypopnea syndrome also increases the presence of MH, especially elevated BP levels at night. Recent studies show that the risk of cardiovascular events in MH is higher than normotension and is equal to or even higher than in sustained HBP. In individuals under antihypertensive treatment, this situation is called masked uncontrolled HBP. The prevalence in the national ABPM registry is around 30% among individuals apparently controlled in the clinic. When the definition of HBP or control is established at 130/80 mmHg, the prevalence of masked HBP can double and reach 60%. The absence of identification of this situation would cause antihypertensive undertreatment.

Target organ damage: MH is associated with cardiovascular and renal events, as well as all-cause mortality. This has been shown in several studies in the general population.[23] MH has often been shown to progress to sustained HBP, even in older people, and confers cardiovascular risk almost like sustained HBP in both the general population and in patients with diabetes and CKD. Most of the previous studies, according to the results of the present analysis, have confirmed that MH had higher cardiovascular risk and similar to sustained HBP. Studies have also shown that the increased risk is independent of the method of out-of-office BP assessment.

In addition to patient-relevant outcomes, studies have also shown a significant association between this masked phenomenon and indirect cardiovascular outcomes, such as left ventricular hypertrophy, increased carotid intima-media thickness, albuminuria, aortic stiffness, high velocity pulse wave, silent and early cerebral infarcts, hypertensive retinal changes in patients with MH.[24]

Diagnosis: Accurate diagnosis of MH depends on reliable BP measurement in the office and out-of-office, through the different devices authorized for BP measurement. In individuals who have normal BP (< 140/90 mmHg) during clinical measurement, it can be stratified into 3 categories:

1. Optimal office BP (< 120/80 mmHg)
2. Normal BP (120-129/80-84 mmHg)
3. High normal BP (130-135/85-89 mmHg)

In people with high normal BP, the possibility of MH should be considered and an out-of-office BP measurement by ambulatory home monitoring or ABPM should be sought. In all categories, evaluation should include clinical history, physical examination, and diagnosis of HBP-mediated target organ damage. Basic screening tests include 12-lead electrocardiogram to look for left ventricular hypertrophy, urine albumin/creatinine ratio, blood creatinine, and estimated glomerular filtration rate to check for retinopathy.

Treatment. MH is a high-risk HBP phenotype and should not be left untreated. Unfortunately, many patients with MH have been excluded from HBP trials due to normal office BP values, leading to a paucity of data on how best to treat MH. No prospective clinical trials have been conducted to assess the effect of MH treatment and its impact on cardiovascular events and mortality. However, consistent evidence pointing to CV risk in patients with MH suggests treatment initiation of MH despite a lack of evidence.

It is reasonable to consider pharmacological management in identified MH patients after optimizing their metabolic profile by treating modifiable risk factors such as obesity, diabetes, OAS, alcohol avoidance, smoking, addressing work, if any, and psychosocial factors. Another

approach is to use antihypertensives to lower ambulatory BP despite the absence of elevated office BP and to monitor response to treatment by periodic ABPM. Several ongoing clinical trials are investigating the impact of antihypertensive treatment in MH. The results of an angiotensin-converting enzyme (ACE) inhibitor are awaited to assess the effect of antihypertensives on clinical and ambulatory BP, proteinuria, and target organ damage in patients with MH. Another large, prospective, multicenter, randomized, 4-year study aims to understand MH treatment based on office and out-of-office ABPM measurements and differences in outcome with a focus on cardiovascular endpoints and events (left ventricular hypertrophy) and renal (proteinuria) including all-cause mortality, CV morbidity and mortality, cerebral morbidity, and mortality. An interventional trial from China also aims to study the role of alisartan isoproxil in the treatment of MH for the protection of the target organs.[25]

4. Phenotypes based on blood pressure variability

We can also find phenotypes in relation to a high BP variability, such as patients with morning, night, or orthostatic HBP and the one that is related to significant elevations in BP with physical effort or emotional changes called by some authors as «reactive».[5,26] For the identification of these phenotypes, the use of ABPM is essential. The main characteristics of these phenotypes are summarized in *Table 4*.

5. Hypertensive phenotypes unresponsive to treatment

We also have patients who do not respond to conventional pharmacological treatment, known as patients with pseudo-resistant HBP and refractory or resistant HBP. These types of patients should generally be referred to specialists in HBP, very common causes

Table 4: High blood pressure phenotypes according to circumstancial high blood pressure.

Phenotype	White coat high blood pressure	Masked high blood pressure
Definition	Normal office blood pressure and normal out-of-office blood pressure.	Factors such as smoking, alcoholism, physical inactivity, exaggerated response to exercise (exercise high blood pressure), interpersonal relationships, mental anxiety and work stress.
Etiology	Psychological factors (stress, anxiety)	Significant association between masked phenomenon and indirect cardiovascular outcomes, such as left ventricular hypertrophy, increased carotid intima-media thickness, albuminuria, aortic stiffness, high pulse wave velocity, silent cerebral infarcts, and early cerebral infarcts, hypertensive retinal changes.
Pathophysiology	Poorly understood. Hypothesis of involvement of the sympathetic and endocrine system.	Variable
Prognosis	Increases the risk of sustained high blood pressure compared to normotensives. Causes target organ damage compared to normotensives. Some studies have found an increased cardiovascular risk compared to normotensive patients.	Increased cardiovascular risk
Treatment	Correction measures in risk factors. Pharmacology should be individualized according to the presence of risk factors and target organ damage.	Pharmacological, studies with ACEI and ARB.

ESH = European Society high blood pressure; ACEI = Angiotensin-converting enzyme inhibitors; ARB = Angiotensin receptor blockers; BB = Beta-blockers.

Table 5: High blood pressure phenotypes according high blood pressure variability.

Phenotype	Nocturnal and day-night variety high blood pressure	Orthostatic high blood pressure	Reactive high blood pressure
Definition	Nocturnal: Mean diastolic > 70 mmHg systolic < 120 mmHg during sleep. Dipper: decrease between 10 - 20%. Hyper-dipper: decrease > 20% Non-Dipper: decrease < 10% Reverse riser or dipper: Lack of descent (0%) or ascent.	Difference between lying and standing position: > 15 to 20 mmHg	Disproportionate increase in BP due to physical exertion or emotional changes. Disproportionate increase in the double product (heart rate x blood pressure) during physical exercise.
Etiology	Obesity, sleep disorders, inadequate antihypertensive therapy.	Unknown	Personality disorders.
Pathophysiology	Due to increased cardiac output and peripheral vascular resistance and in some cases due to sleep apnea.	Autonomic dysfunction.	Increased cardiac output and peripheral vascular resistance.
Prognosis	Increased risk for subclinical cardiovascular and renal damage and increased mortality.	Increased risk of syncope and cognitive impairment.	Increased cardiovascular and renal risk.
Treatment	Treatment of sleep disorder and use of fixed combinations. Chronotherapy?	Evaluate monotherapy.	Psychological and adjustment of pharmacological treatment.

Table 6: Hypertension phenotypes according to responsiveness to treatment.

Phenotype	Pseudo resistant	Resistant
Definition	When treatment control objectives are not achieved with a combination of three drugs at correct doses, including a thiazide-type diuretic, but adequate non-pharmacological measures have not been established or secondary causes have not been ruled out.	When the BP control goals are not achieved despite having established the appropriate non-pharmacological measures and treatment with a combination of three drugs at correct doses, one of which must be a thiazide diuretic.
Etiology	Poor adherence to treatment. Suboptimal doses and/or pharmacological combinations. Improper lifestyle Unidentified secondary cause White or masked coat effect Concomitant use of drugs that stimulate the increase in BP such as NSAIDs, vasoconstrictors, etc.	Multifactorial
Pathophysiology	Unknown	Unknown
Prognosis	Increased cardiovascular and renal risk.	Increased cardiovascular and renal risk.
Treatment	Education and eliminating the cause of pseudo resistance.	Evaluate therapies with the addition of a 4th drug such as spironolactone and rule out a secondary cause. Use alternatives such as renal denervation and carotid stimulation devices in specialized centers.

BP = Blood pressure, NSAID = Non-steroidal anti-inflamatory drugs

of pseudo-resistance should be thoroughly investigated before being designated as resistant *(Tables 5 and 6)*.

Resistant HBP is defined when BP control goals are not achieved despite having instituted appropriate non-pharmacological measures and treatment with a combination of three drugs at correct doses, one of which must be a thiazide diuretic. In these cases, it is often necessary to add a 4th drug such as low-dose spironolactone or refer to specialized centers for invasive therapeutic alternatives such as renal denervation or the implantation of carotid stimulation devices.

Table 7: High blood pressure phenotypes based on urgency or cardiovascular risk

Phenotype	Urgency	Cardiovascular risk
Definition	Major: Severe elevation of diastolic BP > 90 mmHg systolic > 180 mmHg that carries the risk of target organ damage and/or death. Minor: Severe elevation of diastolic BP > 90 mmHg systolic < 180 mmHg that does not carry a risk of target organ damage and/or death.	It depends on the severity of high blood pressure and the association with conventional cardiovascular risk factors and/or metabolic syndrome (MS).
Etiology	Multifactorial	Multifactorial
Pathophysiology	Unknown	Increased cardiac output and vascular resistance, in patients with MS an increase in insulin resistance is observed.
Prognosis	Increased risk of death and cardiovascular and cerebral morbidity.	It depends on severity which is divided into low when the risk of cardiovascular mortality is less than 2%, moderate between 2 and 10%, and high to very high when it is 10%. Patients with diabetes mellitus, target organ damage, frail or MS are considered to be at very high risk.
Treatment	Major: It is treated in an emergency department with specialized treatment mainly with intravenous antihypertensive drugs. Minor: Can be treated in the office with fast-acting drugs and combinations.	Low risk: Changes in lifestyle and monotherapy. Moderate, high and very high risk: Changes in lifestyle and combination therapy. Frail: Changes in lifestyle and monotherapy.

MS = Metabolic syndrome

Table 8: Calculation of total cardiovascular risk (TCR) according to NOM-037-SSA2-2012, for the prevention, treatment and control of dyslipidemias suggests the following levels of total cardiovascular risk.

Level of risk	10-year estimated total cardiovascular risk	Characteristics
Low	< 5%	0-1 risk factors excluding high-risk conditions
Intermediate	5-19%	≥ 2 risk factors excluding high-risk conditions
High	≥ 10%	High-risk conditions: Established cardiovascular disease, diabetes mellitus, severe risk factor, familial hypercholesterolemia, mixed dyslipidemia, familial combined hyperlipidemia, subclinical target organ damage, family history of early stroke, metabolic syndrome, estimated cardiovascular risk ≥ 20%

6. Phenotypes derived by cardiovascular risk or urgency

There are circumstances where HBP can significantly increases the risk of target-organ damage, especially at the brain (malignant), cardiovascular or renal level, called hypertensive urgency. When this damage can be reversible and the life of the patient is not at risk it is called a minor hypertensive emergency or «hypertensive crisis», whereas when this damage puts the patient's life at risk, it is called a major hypertensive emergency or hypertensive «emergency». Cardiovascular risk of patients with HBP depends on the degree of HBP and the association with conventional cardiovascular risk factors and/or metabolic syndrome (MS).

These phenotypes are classified depending on the severity of HBP. It is considered low when the risk of cardiovascular mortality is less than 5% at 10 years, moderate or intermediate between 5-19%, and high to very high when it is greater than 20%. Patients with diabetes mellitus, target organ damage, frail, with MS and other conditions are considered at very high risk *(Tables 7 and 8)*. Increased risk in patients with MS is fundamentally due to abdominal obesity, which leads to carbohydrate metabolism disorders, insulin, and lipid resistance, as well as a proinflammatory and prothrombotic state, along with various other atherogenic factors. Currently available evidence indicates that the diagnosis of MS is more useful in predicting cardiovascular mortality than overall mortality. Finally, estimating the frailty of hypertensive patients, especially older adults, is essential for the treatment to be followed.

Identification of these hypertensive phenotypes can help us decide on the therapeutic approaches to follow. For example, in low-risk patients, changes in lifestyle and monotherapy are started; in patients with moderate, high, and very high risk, changes in lifestyle and combined therapy, while in frail patients changes in lifestyle and monotherapy.

Although we know that there may be many other phenotypes, these are the most common that we face in our daily practice in patients with HBP. Undoubtedly, identifying these phenotypes will allow us to carry out a better daily clinical practice.

REFERENCES

1. Keasley J, Oyebode O, Shantikumar S, Proto W, McGranahan M, Sabouni A et al. A systematic review of the burden of hypertension, access to services and patient views of hypertension in humanitarian crisis settings. BMJ Glob Health. 2020; 5: e002440. Available in: https://doi.org/10.1136/bmjgh-2020-002440
2. Encuesta Nacional de Salud y Nutrición. ENCUESTAS n.d. https://ensanut.insp.mx/encuestas/ensanut2018/informes.php (accessed March 29, 2022).
3. Oseguera HG, Peralta MR, Muñoz JME, Hbpm A group for. Role of home blood pressure monitoring in overcoming therapeutic inertia and improving hypertension control in Mexico. Ann Clin Hypertens. 2018; 2: 017-023. Available in: https://doi.org/10.29328/journal.ach.1001007
4. Kario K. Blood pressure variability in hypertension: a possible cardiovascular risk factor. Am J Hypertens. 2004; 17: 1075-1076. Available in: https://doi.org/10.1016/j.amjhyper.2004.06.021.
5. Hernández HH y, Moctezuma CM, Solís GO, Farías AG de L, Garibay DLL, Pérez MLV et al. Resumen integrado Norma Oficial Mexicana NOM-030-SSA2-2009, para la prevención, detección, diagnóstico, tratamiento y control de la hipertensión arterial sistémica. Rev Mex Cardiol. 2012; 23: 4-38.
6. World Hypertension League | Journal of Human Hypertension n.d. (Accessed March 29, 2022) Available in: https://www.nature.com/jhh/partners/whl
7. Sanchez RA, Ayala M, Baglivo H, Velazquez C, Burlando G, Kohlmann O et al. Latin American guidelines on hypertension. Latin American Expert Group. J Hypertens. 2009; 27: 905-922. Available in: https://doi.org/10.1097/HJH.0b013e32832aa6d2
8. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). Eur Heart J. 2018; 39: 3021-3104. Available in: https://doi.org/10.1093/eurheartj/ehy339
9. Alcocer L, Álvarez-López H, Borrayo-Sánchez G, Cardona-Muñoz EG, Chávez-Mendoza A, Díaz ED et al. Hypertension as a persistent public health problem. A position paper from Alliance for a Healthy Heart, Mexico. Ann Clin Hypertens. 2019; 3: 009-030. Available in: https://doi.org/10.29328/journal.ach.1001015
10. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D et al. 2020 International Society of Hypertension global hypertension practice guidelines. J Hypertens. 2020; 38: 982-1004. Available in: https://doi.org/10.1097/HJH.0000000000002453
11. Sivén SSE, Niiranen TJ, Kantola IM, Jula AM. White-coat and masked hypertension as risk factors for progression to sustained hypertension: the Finn-Home study. J Hypertens. 2016; 34: 54-60. Available in: https://doi.org/10.1097/HJH.0000000000000750
12. Briasoulis A, Androulakis E, Palla M, Papageorgiou N, Tousoulis D. White-coat hypertension and cardiovascular events: a meta-analysis. J Hypertens.

2016; 34: 593-599. Available in: https://doi.org/10.1097/HJH.0000000000000832
13. Hanninen M-RA, Niiranen TJ, Puukka PJ, Johansson J, Jula AM. Prognostic significance of masked and white-coat hypertension in the general population: the Finn-Home Study. J Hypertens. 2012; 30: 705-712. Available in: https://doi.org/10.1097/HJH.0b013e328350a69b
14. Bargalló EV. Hipertensión de bata blanca. Criterios de abordaje y pronóstico. FMC - Form Médica Contin En Aten Primaria. 2020; 27: 515-519. Available in: https://doi.org/10.1016/j.fmc.2020.03.014
15. Nuredini G, Saunders A, Rajkumar C, Okorie M. Current status of white coat hypertension: where are we? Ther Adv Cardiovasc Dis. 2020; 14: 1753944720931637. Available in: https://doi.org/10.1177/1753944720931637
16. Gijón-Conde T, Gorostidi M, Banegas JR, de la Sierra A, Segura J, Vinyoles E et al. [Position statement on ambulatory blood pressure monitoring (ABPM) by the Spanish Society of Hypertension (2019)]. Hipertens Riesgo Vasc. 2019; 36: 199-212. Available in: https://doi.org/10.1016/j.hipert.2019.05.002
17. Chrysant SG. Treatment of white coat hypertension. Curr Hypertens Rep. 2000; 2: 412-417. Available in: https://doi.org/10.1007/s11906-000-0046-7
18. Hozawa A, Ohkubo T, Obara T, Metoki H, Kikuya M, Asayama K et al. Introversion associated with large differences between screening blood pressure and home blood pressure measurement: The Ohasama study. J Hypertens. 2006; 24: 2183-2189. Available in: https://doi.org/10.1097/01.hjh.0000249695.81241.35
19. Huang Y, Huang W, Mai W, Cai X, An D, Liu Z et al. White-coat hypertension is a risk factor for cardiovascular diseases and total mortality. J Hypertens. 2017; 35: 677-688. Available in: https://doi.org/10.1097/HJH.0000000000001226
20. Mancia G, Facchetti R, Parati G, Zanchetti A. Effect of long-term antihypertensive treatment on white-coat hypertension. Hypertens Dallas Tex 1979. 2014; 64: 1388-1398. Available in: https://doi.org/10.1161/HYPERTENSIONAHA.114.04278
21. Thakkar HV, Pope A, Anpalahan M. Masked hypertension: a systematic review. Heart Lung Circ. 2020; 29: 102-111. Available in: https://doi.org/10.1016/j.hlc.2019.08.006
22. Yano Y, Bakris GL. Recognition and management of masked hypertension: a review and novel approach. J Am Soc Hypertens JASH. 2013; 7: 244-252. Available in: https://doi.org/10.1016/j.jash.2013.02.002
23. Babu M, Drawz P. Masked hypertension in CKD: increased prevalence and risk for cardiovascular and renal events. Curr Cardiol Rep. 2019; 21: 58. Available in: https://doi.org/10.1007/s11886-019-1154-4
24. Ibarra-González I, Cruz-Bautista I, Bello-Chavolla OY, Vela-Amieva M, Pallares-Méndez R, Ruiz de Santiago Y Nevarez D et al. Optimization of kidney dysfunction prediction in diabetic kidney disease using targeted metabolomics. Acta Diabetol. 2018; 55: 1151-1161. Available in: https://doi.org/10.1007/s00592-018-1213-0
25. Penmatsa KR, Biyani M, Gupta A. Masked hypertension: lessons for the future. Ulster Med J. 2020; 89: 77-82.
26. Kario K, Eguchi K, Hoshide S, Hoshide Y, Umeda Y, Mitsuhashi T et al. U-curve relationship between orthostatic blood pressure change and silent cerebrovascular disease in elderly hypertensives: orthostatic hypertension as a new cardiovascular risk factor. J Am Coll Cardiol. 2002; 40: 133-141. Available in: https://doi.org/10.1016/s0735-1097(02)01923-x

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Correspondence:
Héctor Galván-Oseguera, MD
E-mail: cardiomedicamx@hotmail.com