INSUFFICIENT CONTROL OF OUT-OF-OFFICE BLOOD PRESSURE: THE PROBLEM OF MASKED UNCONTROLLED HYPERTENSION (REVIEW)

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Abstract

Despite significant advances in the diagnosis and treatment of arterial hypertension (AH), the problem of insufficient blood pressure (BP) control in hypertensive patients is quite acute. According to current guidelines, the effectiveness of antihypertensive therapy is mainly assessed by reaching the target levels of office BP, while masked uncontrolled hypertension (MUCH), which is diagnosed on the basis of insufficient control of out-of-office BP, increases the risk of cardiovascular events. Patients with insufficient out-of-office BP control have an increased risk of cardiovascular events compared to patients with both office and out-of-office BP control, therefore MUCH requires timely diagnosis and correction. This mini-review summarizes the understanding of the nature of MUCH. A particular attention is paid to risk factors and ways of influencing the out-of-office BP control. The article also assessed the important contribution of ABPM to the control of out-of-office BP and to determining the overall risk of MUCH.

Keywords: *masked hypertension, masked uncontrolled hypertension, risk factors, office and out-of-office blood pressure.*

Arterial hypertension (AH) has been and remains the most common non-communicable disease in the world associated with the world's highest rates of cardiovascular morbidity and mortality. It is known about numerous factors contribute to poor blood pressure (BP) control: lack of disease awareness, lifestyle, non-adherence to medication, inadequate treatment, drug hypertension, undiagnosed secondary causes [13, 18, 55].

According to current guidelines, the effectiveness of antihypertensive therapy is mainly assessed by reaching the target levels of office BP, while masked uncontrolled hypertension (MUCH), which is diagnosed on the basis of insufficient control of out-of-office BP, increases the risk of cardiovascular events [58, 62, 67].

As for masked hypertension in general, on the basis of the relationship between office and out-of-office BP, three of the subtypes can be distinguished: masked effect (BP in an untreated subject measured with ambulatory or home BP monitoring (ABPM and HBPM, respectively) is higher than the corresponding normal office BP but within the target), masked hypertension (in an untreated subjects office BP less than 140/90 mm Hg, however at least one of the indicators of out-of-office BP exceeds the diagnostic values for hypertension) and MUCH (in some treated patients in whom the office BP appears controlled to recommended BP targets, but BP is elevated and thus uncontrolled according to out-of-office BP measurements) [38].

It should be noted that patients with masked hypertension and MUCH have an increased risk of cardiovascular events compared to patients with both office and out-of-office BP control [2, 13, 19, 60, 61].

That is why modern guidelines for the diagnosis and treatment of hypertension emphasize the importance of measuring out-of-office BP to confirm the diagnosis of hypertension, as well as indicate the possibilities of this method for assessing the control of antihypertensive therapy [16].

Risk of cardiovascular events in MUCH

Several studies have shown that the presence of MUCH negatively affects the prognosis in patients, but studies that have assessed the global effect of MUCH on cardiovascular outcomes and mortality deserve special attention [3, 5, 8, 11, 40].

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A meta-analysis of six studies using ABPM (12,610 patients with 933 events) and five studies using HBPM (17,742 patients with 394 events) demonstrated a significant effect of MUCH on increased risk of cardiovascular events and mortality from all causes in all ethnic groups (with the highest hazard ratio in studies with Black patients). Therefore, regardless of the cause of MUCH, it is very important to diagnose it on time and then control out-of-office BP, including correcting the risk factors for MUCH [40, 41].

It should be noted that an increased cardiovascular risk in MUCH (compared with normotension and full controlled hypertension) was also confirmed in various single studies and meta-analyses [12, 17, 20, 23, 26, 28].

Results of the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO) study (8,000 untreated subjects from 12 populations) that masked hypertension was associated with similarly increased risk of cardiovascular events as compared to normotensive subjects [7, 14, 38].

Due to the fact that masked hypertension is associated with an increased risk of cardiovascular disease, target organ damage, stroke, and mortality (compared to sustained normotension), 2017 ACC/AHA guidelines, 2018 ESH/ESC guidelines and 2020 ISH guidelines recommend prescribing ABPM to screen for masked hypertension [62, 66, 67].

Data from the Shi Xiaoyang study in the Chinese patient population also confirmed a higher incidence of cardiovascular disease with MUCH compared with patients without masked hypertension [54].

At the same time, compared with non-masked hypertension, patients with MUCH already had significantly more concomitant diseases at the initial level. However, since the cross-sectional design of the study did not allow the authors to confidently answer the question of whether MUCH contributed to these comorbidities or vice versa, additional studies are needed to answer this question, as well as to assess the cardiovascular benefits of patients in improving the control of out-of-office BP [54, 60, 61].

Risk factors of MUCH

Despite the fact that it is not possible to single out any one dominant factor that affects the development of MUCH, the studies have shown that, compared with hypertensive patients with complete control of both office and out-of-office BP, patients with MUCH have a higher constellation of traditional risk factors for cardiovascular diseases and hypertensive target organs damage [31, 35, 49, 68].

Among the factors that affect the MUCH formation, it is possible to distinguish lifestyle features, gender and racial differences, the presence of one or another variant of comorbidity, disturbances in the circadian rhythm of BP, excessive sympathetic activity, an increase in transferrin receptors, as well as factors associated with the choice of antihypertensive therapy and adherence to treatment [40, 41].

Lifestyle and MUCH formation

MUCH formation can depend on various lifestyle factors including psychological stress, smoking and alcohol consumption [13, 41, 42].

In particular, in older people, soon after a heavy meal, there may be a postprandial decrease in BP, so if the measurement of office BP is at this time, then it is likely that masked hypertension is present [39]. At the same time, those who are exposed to mental stress, with office measurements of BP can have normal BP levels, and only with ABPM and in stressful situations, they have an increased BP. Studies show that masked hypertension occurs more often in smokers and people who consume excessive amounts of alcohol [17, 40].

It is noteworthy that people with a sedentary lifestyle, who are obese, usually do not tolerate physical activity during the day, and when the office measurement of blood pressure at rest, BP levels often correspond to pre-hypertension [29].

In addition, in older people (especially males), masked hypertension occurs due to a decrease in the sensitivity of baroreceptors and an increased BP variability. 15. Whereas shortened sleep time (beginning in adolescence) and obstructive sleep apnea are also risk factors for masked hypertension [13, 53].

Sex differences in MUCH formation

Male gender is not only an unmodifiable risk factor for cardiovascular disease in general, but studies show that it is also associated with an increased risk of MUCH in particular [9, 22, 24].

Although the mechanisms underlying sex

differences in MUCH are not fully understood, a number of studies have explained these differences. The study by Siddiqui et al. showed that in MUCH, the level of extraclinical catecholamines and metanephrines in urine was higher than in complete BP control [57]. Since men have higher sympathetic activity than women, this may in part explain high-er prevalence of MUCH in men [22, 24, 57].

The CARDIA cohort, conducted on dif-ferent age groups of patients, showed that male gender was an independent predictor of masked hypertension [45].

Race and MUCH

A number of studies have shown that the prevalence of masked hypertension and MUCH in particular varies significantly depending on the ethnicity of the patients [9, 22, 24, 30, 43, 50].

It should be noted, that in high-normal office BP and additional use of ABPM, masked hypertension was found in more than one third of untreated African Americans and more than 40% of low-income South Africans [13-15, 65].

In particular, the Negroid race is considered as one of the risk factors for masked and MUCH. The results of the Jackson Heart Study of African Americans suggested the presence of isolated nocturnal hypertension in 19% of participants with the mean office BP 124/76 mmHg. In a more recent Jackson Heart Study, in 34% of untreated subjects with normal office BP masked hypertension was established [13-15].

Comorbidities and MUCH

Currently it was proven that the risk of masked hypertension and MUCH, in particular, increases in the presence of a number of comorbidity in patients [6, 9, 13-15, 25, 26].

It should be noted that in one third of Korean adolescents with type 1 diabetes mellitus, an increase in the intima-media thickness of the carotid artery was associated with the development of masked hypertension [25].

In the Brazilian population of patients with type 2 diabetes mellitus and prehypertension, in contrast to sustained normotension, one third of patients had untreated masked hypertension with significant left ventricular hypertrophy and macroproteinuria [26].

The IDACO study found that masked hypertension was present in 29% of patients with type 2 diabetes compared to 19% in the nondiabetic population (adjusted for age, sex and risk factors). It should be noted that 42.5% of diabetics had MUCH [14-15].

The study assessed the prevalence of insufficient out-of-office BP control in chronic kidney disease (CKD) showed that MUCH was observed in 66% of patients with high normal office systolic BP, 33% with normal office systolic BP, and 17% with optimal office systolic BP. This indicates the need for screening ABPM in patients with CKD and prehypertension [14-15].

A Spanish patient registry, which included 2,115 treated hypertensive patients followed for 4 years for cardiovascular events, showed that night BP was the single most important predictor of cardiovascular risk. At the same time, MUCH using ABPM was established in 31% of patients. The clinical characteristics of these patients were advanced age, male gender, smoking history, obesity, diabetes, a longer history of hypertension, which together increased the risk of cardiovascular events in the future [13-15].

Urinary albumin excretion and albumin-creatinine ratio (ACR) are not only markers of glomerular endothelial dysfunction, but have been proven to be associated with the development of MUCH. In particular, the Agarwal study [1] found that MUCH is strongly associated with ACR in CKD, and Verdalles et al. [63] found that albuminuria (measured by ACR) influenced the formation of resistant hypertension. The study of Sung J.H. [59] showed that the ACR was higher in MUCH than in patients with full controlled hypertension, even after controlling cardiovascular disease and CKD.

Another comorbidity that affects the MUCH formation is dyslipidemia. Prejbisz A. et al. [44] found that in MUCH, levels of total cholesterol, LDL-cholesterol and triglycerides were higher than with full controlled hypertension. At the same time, in the studies of Jafar T. et al. [21], differences were shown only in the levels of total cholesterol and LDL-cholesterol in MUCH and controlled AH. In the study of Sung J.H. [59] it was established that all lipids (including total cholesterol, HDL, LDL, triglycerides, and apolipoprotein B) were higher in MUCH compared to full controlled hypertension.

Circadian rhythm disorders and MUCH

Several studies have show that masked

hypertension is associated with a variety of circadian rhythm disturbances [15, 42, 48, 52]. In particular, those patients who smoke, consume excessive alcohol, are exposed to mental stress and do not tolerate physical activity are more likely to have a daytime variant of masked hypertension, whereas with lack of sleep, obstructive sleep apnea, metabolic syndrome, diabetes and chronic kidney disease, nocturnal variant of masked hypertension is most often observed [15].

The meta-analysis of Salles G.F. [48] established that a blunted nocturnal BP decline (as a mean nighttime sleep entity and as a categorical non-dipping subgroup), was a predictor of worse cardiovascular events.

The African American Study of Kidney disease and Hypertension (AASK) trial demonstrated the prevalence of nocturnal non-dipping or reverse-dipping pattern in 70% of patients with MUCH as compared to full BP control [13-15, 42].

The results of our study suggested that as compare to both office and out-of-office BP control in MUCH, circadian rhythm disorders (with a predominance of the non-dipper rhythm) were significantly more common [52].

Sympathetic activity and MUCH

Despite advanced our knowledge on uncontrolled hypertension thanks to the clinical benefits of decrease in BP with renal denervation, central arteriovenous anastomosis, baroreflex activation therapy and carotid body denervation, the variable BP response needs further studies of pathophysiology of poor BP control [18].

The results of the study of Siddiqui M. et al. have shown that patients with MUCH have a higher out-of-clinic sympathetic activity compared with well-controlled hypertension. These data indicate the influence of increased out-of-clinic sympathetic activity on the MUCH formation. Therefore, the question of the possible benefits of drugs and interventional procedures aimed at the activity of the sympathetic nervous system in MUCH remains debatable [55-56].

Another study by these authors showed that patients with MUCH have higher out-of-clinic levels of aldosterone in urine compared with patients with truly controlled AH (this may indicate a higher extraclinical tone of the sympathetic nervous system, that an increase in aldosterone secretion and a higher out-of-clinic BP). It has also been shown that elevated aldosterone levels in MUCH were independently associated with an increased risk of diabetes, suggesting that aldosterone blockade may play a role in lowering high BP and hyperglycemia in these patients [57].

Transferrin receptor and their role in MUCH formation

It is well known that the transferrin receptor plays an important role in the transport of cellular iron, and an increase in transferrin levels can be observed in the presence of iron deficiency. In addition, the association of an increase in transferrin receptors has also been established in a number of cardiovascular diseases (in particular, chronic left ventricular heart failure and pulmonary hypertension) [34, 46, 47, 51].

The study of Sung J.H et al. [59] showed that in MUCH, the transferrin receptors was higher than in patients with full controlled AH (even taking into account demographic variables and comorbidity). Thus, this study showed that the transferrin receptor, along with other factors (such as albumin-creatinine ratio, levels of total cholesterol, high-density lipoproteins, low-density lipoproteins, triglycerides, and apolipoprotein B), is associated with an increased risk of MUCH formation, while MUCH is associated with a very high risk of cardiovascular vascular disease and/or CKD. The results of this study partially explain the lack of efficacy of antihypertensive therapy in certain patient populations [59].

The role of patients and physicians in MUCH prevention and treatment

Considering the fact that in modern recommendations, control of out-of-office blood pressure in patients receiving antihypertensive therapy is not an obligatory component of monitoring the effectiveness of treatment, therefore, MUCH very often remains unrecognized and, accordingly, untreated.

At the moment, under the leadership of the Italian hypertensiologist G. Paratti, a MASTER study (multicenter, multinational study including around 40 clinical centers from different continents) is being carried out in which the strategies for controlling office BP and out-of-office BP (according to ABPM data) are being compared, which in the next few years will be able to answer the question of the effectiveness of one or another variant of BP control in influencing on the prognosis in hypertensive patients [37].

In addition to the fact that MUCH often remains undiagnosed, its high prevalence may be due to the fact that many doctors prescribe “suboptimal" antihypertensive treatment (due to both the doctor’s inertia and his inability to select long-acting antihypertensive drugs, and also due to confusion in optimal levels BP with high in patients cardiometabolic risk) [13-15].

Poor adherence of patients to therapy is considered one of the reasons for the development of MUCH. At the same time, there are controversial data on its effect on poor control of out-of-office BP. In particularly, in the study of Siddiqui M. et al [55], it was shown that patients with masked uncontrolled arterial hypertension did not have significant differences in adherence to therapy compared with patients with good control of office and out-of-office BP.

The results of nine studies with a total of 14,729 participants (11,245 normotensives patients, 3,484 participants with MUCH, 1,984 participants with white-coat hypertension, and 5,143 participants with sustained hypertension) showed that among patients receiving antihypertensive therapy, masked hypertension was associated with a higher the incidence of cardiovascular events than in patients with normal blood pressure and white coat hypertension, and a similar incidence of cardiovascular events in patients with sustained treated hypertension. Therefore, it is important to consider the benefits of early screening and detection of patients with masked hypertension, as well as to assess the goals of BP control in this category of patients based on HBPM and ABPM [36].

It remains not fully understood how the choice of antihypertensive therapy affects the MUCH formation. Despite the fact that a number of studies claim that there is no connection between the MUCH formation and the option of antihypertensive therapy [55, 56], nevertheless, the results of most studies confirm the effect of the choice of antihypertensive therapy on the risk of its formation [4, 10, 27, 29, 32]. In particularly, our recently published study found that in 86.5% of patients with previously established MUCH, strengthening antihypertensive therapy contributed to the achievement of both office and out-of-office BP control [52].

Interesting data on the effect on the prevalence of masked hypertension, sustained hypertension and MUCH in the nondiabetic population was obtained in the recent IDACO study, which compared patients on antihypertensive therapy with those patients who did not receive treatment [14]. It has been shown that both treated patients with MUCH and sustained normotensive patients, there was an increased cardiometabolic risk compared to untreated patients with either masked hypertension or stable normotension. This can be explained by the epidemiological principle that normalization of BP on antihypertensive therapy does not eliminate the burden of life from a previous increase in BP and does not eliminate other cardiometabolic risk factors associated with the hypertensive state. However, at the same time, antihypertensive therapy initiates the transition from stable hypertension to MUCH and then to stable normotension [14-15].

Thus, the analysis of the literature data showed that further research is needed to study the causal biomarker pathways of MUCH and its associations with lifestyle, existing comorbidities, and an antihypertensive therapy option.

Conclusions

Due to superiority of out-of-office BP over clinic BP in predicting prognosis, it is very important to provide ABPM (or HBPM) not only for AH confirmation and also for the control of antihypertensive therapy.

The results of most studies and meta-analyzes have shown that when starting antihypertensive therapy based only on office BP, many patients with sustained hypertension can be converted into the category of MUCH, while not achieving the desired therapeutic result - sustained normotension. At the same time, ABPM is the preferred method for monitoring out-of-office BP, since it provides recording of BP at night time and can determine the overall risk of MUCH (HBPM can be an addition to ABPM).

Given this fact, it is very important that guidelines for the diagnosis and treatment of hypertension, which currently focus on office BP, should reconsider their positions and for patients with elevated office BP it is recommended to receive additional ABPM (or, if not available, HBPM) for determining the true level of BP and improving indicators of poor control of hypertension around the world.

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