Review Article

Masked Hypertension: A New Entity Under Investigation

Arkadia S. Konstantopoulou, Ioannis K. Papargyriou, Eleni S. Antoniadou, Pagona S. Konstantopoulou, Dimitrios E. Papadogiannis

1st Propedeutic Department of Internal Medicine, University of Athens, Laiko Hospital, Athens, Greece.

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Address:
Dimitrios Papadogiannis

27 Ikarias St.
145 78 Ekali, Athens,
Greece
e-mail:
d_papadogiannis@yahoo.com

Arterial hypertension is as common in Greece as in other developed countries and affects around 25% of the adult population.[1] The rates of recognition, treatment and control of hypertension in the Greek population[2] are similar to those found by studies in other developed countries, as follows:

- 22% under treatment, controlled.
- 30% under treatment, not controlled.
- 11% diagnosed but untreated.
- 37% undiagnosed.

Hypertension is characterised by large variations, both within the same day and from one day to another.[3] Consequently, its diagnosis must be based on multiple blood pressure (BP) measurements performed on separate occasions. BP may be measured by a doctor or nurse in the doctor's office, outside the clinic or at home by the patient or a relative, or automatically during 24-hour ambulatory recording.

Until recently, the diagnosis of arterial hypertension was based on measurements in the doctor's office. Many studies have shown that these measurements are of secondary prognostic value compared to those made outside the clinic, although there are differing views as to the prognostic role of the three methods. Some prefer 24-hour monitoring[4-7] while others favour measurements at home.[8-11] However, there are indications, such as those from the PAMELA study (Pressione Arteriose Monitorate E Loro Associazioni), that the overall prognostic capability is no greater for measurements outside the doctor's office than for those inside.[12]

The introduction of 24-hour BP monitoring and the widespread use of home BP measurements for the diagnostic evaluation of arterial hypertension have led to the following system for classifying patients.

1. Normal BP in the doctor's office and normal BP outside the clinic (24-hour monitoring).
2. High BP both in and outside the clinic (24-hour monitoring).
3. High office BP and normal BP outside the clinic (24-hour monitoring).
4. Normal office BP and high BP outside the clinic (24-hour monitoring).

The two first categories of patients are described as normotensives and hypertensives, respectively, since the in and out of office measurements agree. However, much interest has been drawn to patients where there is disagreement between the in-office and out of office measurements.

The third category above refers to the phenomenon known as "white coat hypertension", although the more descriptive and less mechanistic term, "isolated office hypertension", should be preferred. The phenomenon has been studied extensively and there are guidelines for its diagnosis, investigation and treatment.[13]

Until today, little attention has been paid to the fourth category of patients, with normal office BP and elevated pressure outside the clinic.[14] The following terms have been proposed to describe this condition:[15]

- Masked hypertension (since it is not diagnosable by BP measurements in the doctor's office).
- Isolated ambulatory hypertension (since it can be diagnosed by 24-hour ambulatory monitoring).
- Reverse white coat hypertension.
- White-coat normotensives.

Based on measurements, first in the doctor's office and secondly at home, or during ambulatory monitoring, two definitions have been proposed: office BP <140/90 mmHg and a mean daily pressure on 24-hour monitoring ≥135/85 mmHg; or office BP <140/90 mmHg and a mean of home measurements ≥135/85 mmHg. Either of the out-of-office measurement methods may be used for diagnosis, but for the long-term follow up of these patients home measurements are preferred because of their ease and low cost.[8]

What evidence is there, though, that patients exhibiting the phenomenon of masked hypertension need special attention?

First, for the masked hypertension phenomenon to be considered reliable its reproducibility must be proved; so far, few studies have examined this criterion.[15,16]

In addition, an important question is the frequency of occurrence of the phenomenon. Relevant studies have produced conflicting results. In one study of 319 clinical normotensives, it was found that 23% exhibited the masked hypertension phenomenon, defined as mean daytime BP on 12-hour monitoring >135/85 mmHg and office BP <140/90 mmHg.[16] Another study found that 36 of 267 male patients (13.5%) had masked hypertension, defined as diastolic office BP <85 mmHg and mean daytime diastolic BP from ambulatory monitoring >85 mmHg.[17]

Two cohort studies also reported the phenomenon. The first was the Ohasama study, which was carried out in a small Japanese town and included 705 individuals. It showed that 10.2% of those with normal office BP levels, namely <140/90 mmHg, were "marginal hypertensives", with a mean BP from ambulatory monitoring >133/78 mm Hg, while a further 3.2% were "real hypertensives", with mean monitored BP >144/85 mmHg.[18] The second study was the PAMELA study, which included 3200 Italians, 9% of whom had masked hypertension, defined as normal office BP <140/90 mmHg, mean BP from 24-hour ambulatory monitoring >125/79 mmHg, and from home measurements >132/83 mmHg.[19]

Liu et al attempted to investigate the masked hypertension phenomenon and reported its presence in 61 individuals from a total of 295 clinical normotensives studied. Thus 21% of the study population met the criteria of office BP <140/90 mmHg and mean daytime monitored BP >134/90 mmHg.[20]

Two newer studies investigated masked hypertension in children and the elderly. The former study included 535 children, mean age 10.2 years, and found 45 (7.6%) with masked hypertension. Of those 45, 38.2% remained with masked hypertension, while 8.8% progressed to become true hypertensives.[21] The second study investigated 578 elderly individuals, mean age 70 years, and found that 82 (14%) had masked hypertension, defined as office BP <140/90 mmHg and mean morning BP from 24-hour monitoring >135/82 mmHg.[22]

It is clear, then, that the various studies show different rates of occurrence of the masked hypertension phenomenon. This could be due to differences between the populations studied, or to the different criteria used for diagnosis. Even so, it is important to discover the characteristics of individuals with masked hypertension that might be aetiologically related with the occurrence of the phenomenon.

Masked hypertension is equally common in both sexes. Its incidence is greater when the diagnosis is based on measurements of systolic, rather than diastolic or mean BP. There is no difference in frequency between treated and untreated patients, but it is even more common in hypertensives whose BP has been controlled satisfactorily to ≤140/90 mmHg.[4]

Various studies have also investigated demographic, epidemiological and laboratory parameters, as well as differences in way of life. Special emphasis is placed on those who a have a familial history of arterial hypertension, or other cardiovascular risk factors, such as central obesity, diabetes mellitus, male sex, past or present smoking or alcoholism.[5,16] As far as age is concerned, one study found that in 72% of women and 86% of men aged 42 years the systolic BP obtained from ambulatory monitoring was higher than the in-office measurement ($p=0.001$), while for patients aged 72 years the respective percentages were 38% ($p=0.003$) and 51% (p: NS). The authors interpreted the result as being due to differences in the daily activities between the two age groups; however, the criteria used were not diagnostic for masked hypertension.[23]

In a study by Pierdomenico et al, which included

742 hypertensives under treatment, 126 of them had masked hypertension, while 146 had isolated office hypertension. Smoking was more common in the patients with masked hypertension, as was coffee consumption, whereas alcohol consumption and the use of anti-inflammatory drugs was lower. There were no differences related to professional situation or drug therapy.[5]

Selenta et al investigated the phenomenon in 319 patients, using a questionnaire that examined various psychological parameters (daily stress, hostility, anger, depression, social support), but found no differences between normotensives and individuals with masked hypertension. The authors claimed that their study was incomplete and that further investigation of the patients' psychological profile was needed.[16]

Patients with masked hypertension would be expected to show more frequent target organ lesions than real normotensives, and more than patients with isolated white coat hypertension. This is because, according to the definition of the phenomenon, they are patients who are hypertensive but whose diagnosis is delayed because of their normal BP values when they visit the doctor. The first study of this question showed that the left ventricular mass was 73 g/m^2 in real normotensives, 86 g/m^2 in patients with masked hypertension and 90 g/m^2 in real hypertensives. It also showed that 15% of real normotensives had atheromatous plaque in the carotid arteries, whereas for masked hypertension patients and real hypertensives the incidence was similar at around 28%.[20] More recently, in the PAMELA study referred to above, the left ventricular mass was 91.2 g/m^2 in patients with masked hypertension, similar to the 94.2 g/m^2 in real hypertensives, whereas in real normotensives it was 79.4 g/m^2.[19] The incidence of left ventricular hypertrophy was related with the absolute BP values obtained from 24-hour monitoring and in-office measurements, but not with the difference between them.[4]

The cardiovascular morbidity and mortality in masked hypertension are already under investigation. A number of studies have shown the powerful prognostic value of 24-hour BP monitoring in relation to cardiovascular morbidity and mortality.[24] In the study by Björklund et al referred to above, the studied patients were followed for 8.4 years until the age of 70 years, during which period 72 fatal and non-fatal events were recorded, with an incidence of cardiovascular events of 3.14% in the real hypertensives, 2.74% in patients with masked hypertension, and 0.99% in real normotensives.[22]

The SHEAF study (Self-measurement of blood pressure at Home in the Elderly: Assessment and Follow-up) included 4939 patients under antihypertensive treatment, men and women aged over 60 years, with mean follow up 3.2 years. The patients made three morning and three afternoon measurements at home on four successive days. Based on the home measurements, the study showed that for each 10 mmHg increase in systolic pressure the risk of a cardiovascular episode increased by 17%, while for each 5 mmHg increase in diastolic pressure the risk increased by 11.7%. A similar analysis of the in-office measurements found no significant increase in cardiovascular risk. In comparison with controlled hypertensives, the relative risk for a cardiovascular episode was 2.06 (95% CI 1.22-3.47) in patients with masked hypertension, 1.18 (95% CI 0.67-2.10) in patients with isolated office hypertension, and 1.96 (95% CI 1.27-3.02) in uncontrolled hypertensives.[9]

In conclusion, it is clear that the phenomenon of masked hypertension is one of great importance. A significant number of patients will continue to evade the usual diagnostic check as long as it is based solely on measurements in the doctor's office. It has thus been proposed that all patients who show normal BP values in the clinic should be checked for masked hypertension using 24-hour monitoring or home measurements.[10]

However, if this is not feasible it is absolutely essential that the possibility of masked hypertension should be investigated in all patients who have normal office BP but also have target organ lesions. The overall cardiovascular risk can be usefully calculated and necessary recommendations can be made for lifestyle changes and the start of drug therapy when this is judged beneficial.[25]

As regards an interpretation of the phenomenon, it is likely that during BP measurement the physician's presence creates an atmosphere of security and trust, in contrast to pressures that affect the patient's situation at work or at home, with the result that BP measurements are lower in the doctor's office.

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