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Franz Volhard lecture: should doctors still measure blood pressure? The missing patients with masked hypertension

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Abstract

The traditional reliance on blood pressure (BP) measurement in the medical setting misses a significant number of individuals with masked hypertension, who have normal clinic BP but persistently high daytime BP when measured out of the office. We suggest that masked hypertension may be a precursor of clinically recognized sustained hypertension and is associated with increased cardiovascular risk compared with consistent normotension. We discuss factors that may contribute to clinic–daytime BP differences as well as the changing relationship between these two measures over time. Anxiety at the time of BP measurement and having been diagnosed as hypertensive appear to be two possible mechanisms. The identification of individuals with masked hypertension is of great clinical importance and requires out-of-office BP screening. Ambulatory BP monitoring is the best established technique for doing this, but home monitoring may be applicable in the future.

Keywords

blood pressure measurement; masked hypertension; white coat hypertension

The general recommendation for blood pressure (BP) measurement for the clinical detection of hypertension is that BP should be recorded in a clinical setting. This procedure has been widely endorsed by organizations such as the American Heart Association [1], the Joint National Committee [2], and the European Society of Hypertension [3]. It has always been assumed that the brief but controlled measurement of BP made in the traditional clinic setting correlates well with the average or typical level of BP that occurs over weeks and months (sometimes regarded as the ‘true’ BP [4]) and, most importantly, predicts the long-term effects of hypertension. Although this assessment method has represented the standard of care for many years, evidence has been accumulating over the past 20 years, both from ambulatory BP (ABP) and home-monitored BP measured outside the clinic setting, that the average BP measured over days and weeks gives a better prediction of risk of cardiovascular morbidity than conventional clinic measurement [5]. Despite the fact that cardiovascular risk increases progressively as BP increases from relatively low levels, hypertension, for many years, has arbitrarily been defined as a clinic BP above 140/90 mmHg, and the equivalent

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daytime level measured away from the medical environment by ambulatory (or home) monitoring has been generally accepted as 135/85 mmHg [1,3,6,7], although these levels may be changed in the future [8].

Although the majority of people who have hypertension that also exists during daily life are detected by clinical measurement, there are two important groups whose identification as being hypertensive is different by the two methods (i.e., measured in the clinic or away from it): first are the individuals whose clinic BP is high but ABP is normal (the white coat hypertensive patients) and second are the individuals whose clinic BP is within the normal range but out-of-office BP is persistently high (the so-called masked hypertensive patients). In the present study, we will not discuss the white coat hypertensive patients, who are not a major clinical problem, as they tend to be at a relatively low risk of cardiovascular disease and are already identified (on the basis of their high clinic measurements) as having BP that needs to be followed. In contrast, the masked hypertensive patients create more of a clinical problem: they tend to be young and are at an elevated risk of cardiovascular disease, but their diagnosis of hypertension is missed by the traditional criteria.

The limitations of clinic blood pressure measurement

The small number of readings that are taken in the clinic setting (typically, two or three per visit) have always been assumed to represent the average level of BP that occurs between clinic visits, that is, often a period of a month or longer. There are three main sources of error that reduce the agreement between clinic BP and the true BP level. The first is impaired technique, such as rounding to the nearest 10 mmHg rather than to 2 mmHg (as recommended). The second is the limited number of readings that can be taken, which limits the accuracy of clinic BP because of spontaneous BP variability both during a single visit and, especially, between clinic visits. This was demonstrated many years ago by Armitage and Rose [9], who took two BP readings in an office setting at 2-week intervals in predominantly normotensive individuals. There was substantial spontaneous variation between 95 and 128 mmHg over three consecutive visits. The implication of this, for hypertensive patients, is that the assessment of antihypertensive treatment using repeat clinic measurements is very inaccurate. This limitation could be reduced by either increasing the number of visits or the number of readings per visit. The third source of error, which we believe is the most important, both because of its magnitude and because of its systematic nature, lies in the psychological and situational determinants of BP that affect the difference between clinic BP and ABP. The traditional, and still widely held, view of this error has been that clinic BP tends to be higher than true BP; thus, it was recognized by Ayman and Goldshine [10] in 1940 that BP recorded at home either by the patient or a family member might be less than the doctor's readings by 20 mmHg or more.

However, the relationship between clinic BP and ABP varies consistently according to the hypertensive status of the individual. In normotensive persons, clinic BP tends to be lower than the BP measured at work or home [11]. Because clinic BP is measured with the individual seated quietly at rest, whereas work and home BPs are measured during mild physical and mental activity, this difference is not surprising. In contrast, the average clinic BP in the established hypertension group is consistently higher than the average work and

home BP levels. In other words, the white coat effect (WCE), which has been defined as the difference between clinic BP and daytime average ABP, is typically negative in normotensive individuals and positive in the hypertensive patients. This raises the issue as to why there should be such a consistent difference between the two groups. We suggested, some years ago, that the reason might be that hypertension is traditionally diagnosed on the basis of high clinic BP [11], so many individuals who show an exaggerated WCE will be labeled as being hypertensive. Similarly, individuals who exhibit an absent or negative WCE will tend to be classified as normotensive, but a subset of them will be masked hypertensive.

Epidemiological surveys of the general population have shown that there is a progressive increase in both daytime and nighttime BP with age, as expected. However, several studies that have included both ABP and clinic BP in general population participants, rather than those seen in a medical setting, have found that clinic BP shows a much steeper rise with age than daytime BP [12–16]. Results from one of these studies [12] are displayed in Fig. 1. Because clinic measurement is made with participants seated at rest, it is expected that the readings will be somewhat lower than the average of daytime BP, which includes both physical and mental activity. As shown in the figure, this is apparent in younger persons, those below 40 or 50 years of age, but in older persons, clinic BP shows progressive increases such that it greatly exceeds the average daytime BP. If the increased clinic BP with age was due to a nonspecific increase in BP reactivity to physical or psychological stimuli, one would expect to see the average daytime BP increase more than nighttime BP, but this does not occur, and studies of reactivity to mental stress have not identified an age-related increase [17]. This figure also suggests that the prevalence of white coat hypertension increases markedly with age.

Characterization of individuals with masked hypertension

Individuals can be classified into four groups according to their levels of clinic and out-of-clinic BP; the latter measured by either ambulatory or home monitoring (Fig. 2). The 5 mmHg difference allows for the fact that clinic BP tends to be higher than out-of-clinic BP in clinic samples of patients and is the conventional recommendation [1,3,6], but it has ignored the fact that the WCE changes markedly with age (Fig. 1). Sustained hypertensive and true normotensive groups are of relatively little interest here because they are classified in the same way by both criteria. Of more interest are the two groups that are identified as hypertensive by one, but not the other, measure.

The white coat hypertension group consists of individuals who are identified as hypertensive only by the conventional clinical BP screening and are clinically important only because they are at a lower risk of cardiovascular morbidity than suggested by their clinic BP. The group we want to focus on consists of those who have masked hypertension, that is, those who are hypertensive during daily life (measured by either ambulatory or home monitoring) but whose office BP is within the normal range, so that by traditional criteria they are assumed not to need further BP evaluation. The definition of such individuals is that they have a persistently normal clinic BP and elevated ABP. We first became interested in this group when we observed that these individuals had signs of target organ damage [18]. We assessed two measures of target organ damage and compared their prevalence in individuals

with masked hypertension with the rates in those with true normotension and sustained hypertension. In those with masked hypertension, whose clinic BP was in the normal range but whose ABP was high, both the average left ventricular mass index and the prevalence of carotid plaque indicated target organ damage levels that were similar to those with sustained hypertension and more extensive than in truly normotensive individuals [18].

We and others have looked at the long-term prognosis of individuals with masked hypertension in an international database, which includes data from the New York, Ohasama (Japanese), and the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (Italian) studies. In these three databases, there were 1272 participants with a normal clinic BP (<140/90 mmHg), of whom 376 had high ABP (>135/85 mmHg during the day), whereas others were normotensive by both criteria. During the follow-up period, the rate of cardiovascular events was significantly higher (hazard ratio, 2.26; $P < 0.009$) in the masked hypertension group than in the true normotensive one. Other studies have also found that individuals with masked hypertension are at increased risk for cardiovascular events [19–22].

An important issue concerns the prevalence of masked hypertension in the general population. There have been at least five studies, three in population-based samples and two, including one of our own [18], in selected participants. The three general population studies [19,21,23] have found that the prevalence of masked hypertension was 10, 9, and 14% of the general population. The two studies that included some participants in medical settings found much higher prevalences (21 and 23%) [18,24]. If we just look at the population studies, it appears that about 10% of the general population meets the criteria for masked hypertension.

There are many reasons why clinic and daytime BPs can differ from each other. For example, anxiety in the physician's office might cause a temporary elevation in clinic BP that is absent for most daytime BP readings, causing a positive WCE. On the contrary, physical activity during the day could cause elevations in daytime BP, relative to clinic BP readings, causing a masked hypertension effect. We discuss these and other possibilities below.

Determinants of the difference between clinic and out-of-office blood pressure

In order to assess the difference between clinic and out-of-office BP and the psychological factors that might determine this difference, we recruited participants both with and without a history of hypertension, none of whom were taking any antihypertensive medications [25]. We measured ABP in these participants for 36 h and measured casual BP on 2 days. On day 1, readings were taken in a laboratory that was not part of the clinical setting, and on day 2, readings were taken in the traditional clinical setting; these included readings taken by a research assistant in the waiting room and the examination room and readings taken by the physician in the examination room. All readings were taken with an ABP monitor, except those taken by the physician using a mercury column sphygmomanometer and stethoscope. The participant was taken to the examination room 10–15 min after the waiting room

readings were taken. The research assistant took readings in the examination room before and after the physician arrived to take three BP measurements. The WCE was defined as the average of the three physician readings minus the average awake ABP. Anxiety was assessed at multiple points throughout the day 2 clinic visit using a visual analog scale (VAS). The VAS consisted of a horizontal 6-inch line marked ‘0’ (none) at the left end and ‘100’ (a great deal) at the right. Participants were instructed to make a mark on the line indicating their level of anxiety at that moment. Participants completed the VAS a total of eight times throughout the day 2 visit, including in the waiting room, in the examination room before the physician entered, in the examination room while the physician was present, and in the examination room after the physician left the room. This 2-day assessment was conducted three times at 1-month intervals; BP and VAS scores were averaged over the three assessments. Participants also completed three commonly used measures of general anxiety: the brief symptom index–anxiety subscale, the Spielberger trait anxiety index, and the Taylor manifest anxiety scale.

We performed analyses in 238 participants: 35% true normotensive, 37% sustained hypertensive, 9% white coat hypertensive, and 19% masked hypertensive individuals [25]. As is shown in Fig. 3, there are interesting differences in the measures between the four groups. The most conspicuous one is that in the sustained hypertensive group, the physician's reading, by definition, and the other clinic measures are all above the clinic threshold of 140 mmHg and higher than the daytime average, whereas in the true normotensive group, in whom the physician's reading must be below 140 mmHg, clinic measures are not higher than the daytime average. These differences are even more marked in white coat hypertensive and masked hypertensive groups, who are, of course, defined by the physician-taken readings as well as ABP. Data shown in Fig. 3 suggest that using the nonphysician clinic readings might be better for making the clinical diagnosis and estimating the level of ABP than the physician's measurements as has been suggested using automated devices [26].

A major issue is why the four groups of participants show variable response to the clinic setting, and whether differences in anxiety could explain BP differences. As noted above, we assessed two types of anxiety measures in these participants. The brief symptom index, Spielberger and Taylor scales measure anxiety in general, whereas a VAS was used to measure (current) anxiety at the moment of each BP measurement. Consistent with previous studies [27,28], the four groups did not differ on any of the general anxiety measures; the only measure that differed by diagnostic category was the VAS anxiety measure ($F(3237) = 6.4$, $P < 0.0005$). The VAS score was highest in the white coat hypertensive group (30.6, on a 0–100 scale), elevated in the sustained hypertensive group (24.5), and low in the true normotensive group (14.5) and the masked hypertensive group (15.9). Although we cannot rule out the possibility that VAS is simply a more sensitive assessment of anxiety, these results strongly suggest that group differences in anxiety are specific to the clinical setting and do not reflect group differences in general anxiety levels.

The VAS anxiety levels reported by participants at various times during the clinic visit are shown in Fig. 4. There are basically two patterns: sustained hypertensive and white coat hypertensive groups score high on anxiety throughout the visit, and true normotensive and

masked hypertensive groups score low. In addition, planned comparisons of changes in anxiety between each time point show that the white coat hypertensive group reported more marked increases in anxiety than the other three groups immediately after the physician took their BP.

When we compared the four groups of participants, there was a marked parallelism between the WCE and the level of anxiety at the time of BP measurement. Thus, the two groups that had a negative average WCE (the mean for true normotensive group, −1.8 mmHg, and for masked hypertensive group, −5.3 mmHg) had low levels of momentary anxiety, whereas the two groups with a positive average WCE (sustained hypertensive group, +6.9 mmHg, and white coat hypertensive group, +15.4 mmHg) had consistently higher levels of momentary anxiety during the clinic visit on day 2. Overall, the WCE was significantly correlated with the anxiety ratings made throughout the clinic visit (r from 0.26 to 0.37, $P < 0.001$, systolic; r from 0.16, $P < 0.05$ to 0.29, $P < 0.001$, diastolic).

Effects of hypertension diagnosis on the relationship between clinic and ambulatory blood pressure

Another approach we used to analyze the difference between clinic BP and ABP was to classify participants according to whether or not they were hypertensive based on ABP and whether or not they had ever previously been told that they were hypertensive [29]. Thus, there were four groups again, but they were classified differently than the ABP–clinic BP groups described above: those who were normotensive on ABP and had not been diagnosed as hypertensive (66 participants); those who were hypertensive on ABP and had been previously diagnosed (72 participants); those who were hypertensive on ABP but had ‘not’ been diagnosed (47 participants with either undetected sustained or masked hypertension); and those who had normal ABP but had previously been diagnosed as hypertensive (29 participants either misdiagnosed because of white coat hypertension or who misunderstood previous BP results).

When we examined the difference between clinic BP and ABP (the WCE) in the four groups, we found that it was not related to whether or not participants were truly hypertensive (by the ABP level) but was related to the previous diagnosis of hypertension. Thus, a positive WCE was present in the two groups of participants who had previously been labeled as hypertensive (+1.0 mmHg in the diagnosed hypertensive group and +6.0 mmHg in the ABP normotensive group who had previously been (mis)diagnosed), and a reversed WCE was present in the two groups who had never previously been labeled (−5.3 mmHg in the undiagnosed normotensive group and −3.5 mmHg in the undiagnosed hypertensive group). The VAS anxiety scores at the time of BP measurements followed the same pattern: the two groups that had been previously labeled as hypertensive reported the greatest anxiety (25 in the diagnosed hypertensive group and 33 in the normotensive group who had previously been diagnosed), and the two groups that had not been labeled reported the lowest anxiety (11 in the undiagnosed normotensive group and 15 in the undiagnosed hypertensive group). The WCE was significantly correlated with the mean VAS anxiety score (r=0.29 and 0.26, both $P < 0.001$ for systolic and diastolic WCE, respectively).

The data indicate that, on average, persons who had in the past received a diagnosis of hypertension – whether or not they were actually hypertensive according to their ABP measurements – tended to have substantially higher anxiety scores and exhibit a substantially higher WCE than those who had never received a diagnosis of hypertension (whether or not they were actually normotensive according to their ABP measurements). The analyses indicated that for both anxiety and the WCE, differences between previously diagnosed and never diagnosed participants were significant after controlling for age, sex, and awake ABP: $F(1208) = 15.30$, $P < 0.001$ (anxiety); $F(2207) = 11.64$, $P < 0.001$ (WCE, multivariate analysis of variance test for systolic and diastolic BP; the effect was significant for systolic and diastolic BP in univariate analyses, both $P < 0.001$).

Another issue concerns the extent to which the relationship between clinic BP and ABP over time relates to having been diagnosed as hypertensive. When we looked at the relationship for the overall data in our study, we found a pattern that was almost identical to the one shown by Schettini *et al*. [12] (Fig. 1), in which clinic BP exhibits a much larger change with age than ABP, such that daytime ABP tends to be higher than clinic BP up to the age of about 50 years, above which the clinic BP increases progressively higher than ABP with further increases in age.

However, when we separate people according to whether or not they were ever diagnosed as being hypertensive or not, we see a noticeably different picture. As shown in Fig. 5, in the participants who had not been diagnosed as being hypertensive, clinic BP remains lower than ABP in younger people and does not exceed it in older people. However, in those participants who have been labeled as being hypertensive, the pattern is very different. As expected, BP readings are all higher, but the important difference is between clinic BP and ABP in that over the age of 50 years, clinic BP tends to substantially overestimate the ABP. These results are consistent with the hypothesis that the diagnosis of hypertension causes future clinic BP readings to be higher than they would otherwise be.

Implications for masked hypertension

The main finding is that the traditional technique for measuring BP using office measurements to screen and identify people with hypertension misses a substantial number of individuals who have normal clinic but elevated daily BP, whom we would label as having masked hypertension and who probably include at least 10% of the general adult population. The fact that they may often be young, and at a high risk of cardiovascular morbidity, increases the importance of diagnosing them at an early age. A key finding is the age-related difference between clinic BP and ABP, which explains why masked hypertension is detected in relatively younger people and white coat hypertension in older ones. In the observational study of the determinants of the WCE described above, we found two things. First, a large and positive WCE is not related to generalized anxiety but to increased anxiety at the time of BP measurement. Second, one of the predictors of a positive WCE was having been previously given a diagnosis of hypertension.

These findings are consistent with the WCE being a conditioned anxiety response that is relatively specific to the clinic setting and, therefore, unlikely to have prognostic

significance. The apparently gradual rise in clinic BP with age in relation to the daytime average could be explained by the gradually increased likelihood of having adverse experiences during medical encounters, which would generate a positive WCE. Thus, in one individual, we might expect more of a step change in clinic BP, but this would not be apparent in population studies. Perhaps the best demonstration that this can occur comes from a study performed by Rostrup and coworkers [30–32] in a group of 32 young Norwegian men who were found to have high BP on screening for military service. Participants were divided into two groups, one of which was informed that their pressures were high, whereas the other was not. Two weeks later, they returned for a second series of measurements, which included reactivity testing. The group that had been labeled as being hypertensive showed a persistently higher BP throughout the 45 min of testing than the uninformed group. Ambulatory blood pressure monitoring (ABPM) was not performed.

The concept that the WCE is a conditioned anxiety response also has important implications for the phenomenon of masked hypertension, which is relatively new [33] and has not yet found its way into the mainstream clinical hypertension literature. If it is accepted that the ‘natural’ condition is that clinic BP is lower than daytime BP, it could be argued that masked hypertension is not an aberrant condition or interesting subtype of hypertension but represents the true ‘natural history’ of hypertension, in which there is not a disproportionate rise in clinic BP with age in relation to other measures of BP. Thus, the other terms that have been used to describe it, such as ‘white coat normotension’ and ‘reverse white coat hypertension’, seem quite inappropriate in this context [34]. Thus, masked hypertension may be an intermediate stage between true normotension and sustained hypertension [35]. There is some evidence for this: in a prospective Italian study of young adults who were evaluated with both clinic BP and ABP, none of whom had been on antihypertensive treatment, it was found that participants identified as having masked hypertension had double the risk of developing sustained hypertension over the next 6 years compared with truly normotensive participants [36]. Also, a study of 592 Spanish children and adolescents found that 7.6% had masked hypertension [37]. These individuals were more likely to have a parental history of hypertension than the normotensive children and were more likely to progress to sustained hypertension over a 3-year follow-up.

Identification of patients with masked hypertension

A major issue is how patients with masked hypertension can best be identified. First, it is clear that traditional clinic BP measurement cannot by itself identify it, and that out-of-clinic BP needs to be measured. This raises two issues: the first is what BP measurement process should be used, and the second is what levels of clinic BP should be used to recommend screening. An important related issue is the extent to which masked hypertension overlaps prehypertension, a concept that was first introduced in the latest version of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) recommendations on the management of hypertension (JNC 7, published in 2003 [2]), and which was defined as a clinic BP of 120-139 mmHg systolic or 80–89 mmHg diastolic or both. The idea was that such individuals are at increased risk of developing hypertension (≥140/90 mmHg for clinic BP) and cardiovascular disease. Although there is agreement that prehypertensive individuals are at increased risk of cardiovascular events compared with

truly normotensive ones [38], it is not clear to what extent this is because of BP itself. Thus, in an analysis of the National Health and Nutrition Examination Survey (NHANES) data, Mainous *et al.* [39] found that the excess risk disappeared if the effects of concomitant risk factors were accounted for. The practical problem with the concept of prehypertension is that it affects so many people; a recent analysis of the NHANES data found that 39% of adults in the United States over the age of 20 years are normotensive, 31% prehypertensive, and 29% hypertensive [40]. Thus, only a minority of Americans has a normal BP by these criteria.

One of the major themes of this article is that masked hypertension is a precursor of sustained hypertension and again, similar to prehypertension, is associated with increased risk. It comes as no surprise that clinic BPs of persons with masked hypertension tend to be in the high normal range, so if we used only clinic BPs, most of them would be regarded as having prehypertension. This leads to the proposal that masked hypertension may represent a high-risk subset of prehypertension, a concept that has obvious public health import, given that there are about 100 million Americans who are classified as being prehypertensive. On the basis of the few population studies of masked hypertension, we have estimated that the number of Americans with it may be 20 million, a still large but much more manageable number. We believe that the highest probability of masked hypertension occurs in persons whose clinic pressure is just below the upper limit of normal BP.

For the detection of masked hypertension, we believe that home monitoring is likely to prove more cost-effective than ambulatory monitoring, and we have recently endorsed the routine use of home monitoring with the support of the American Heart Association, the American Society of Hypertension, and the Preventive Cardiovascular Nurses Association [41]. The European Society of Hypertension will publish a similar statement. However, the use of home monitoring for diagnosing masked hypertension has not been extensively studied [42].

Conclusion

The traditional reliance on BP measurement in the medical setting misses a significant number of individuals with masked hypertension, which we suggest may be a precursor of clinically recognized sustained hypertension and is associated with increased cardiovascular risk in these individuals compared with that in consistently normotensive individuals. Out-of-office BP screening needs to be done to identify individuals with masked hypertension. ABPM is the best established technique for doing this, but home monitoring may be applicable in the future.

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Abbreviations

ABP	ambulatory blood pressure
ABPM	ambulatory blood pressure monitoring
JNC	Joint National Committee
MANOVA	multivariate analysis of variance
NHANES	National Health and Nutrition Examination Survey
VAS	visual analog scale
WCE	white coat effect

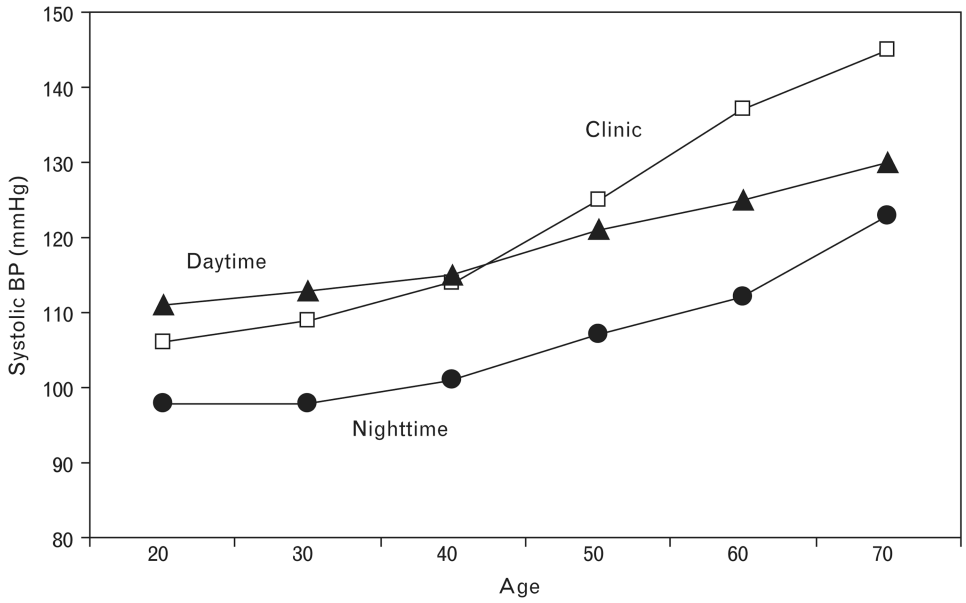

Fig. 1.

Changes in blood pressure with age in a population survey. BP, blood pressure. Adapted from [12].

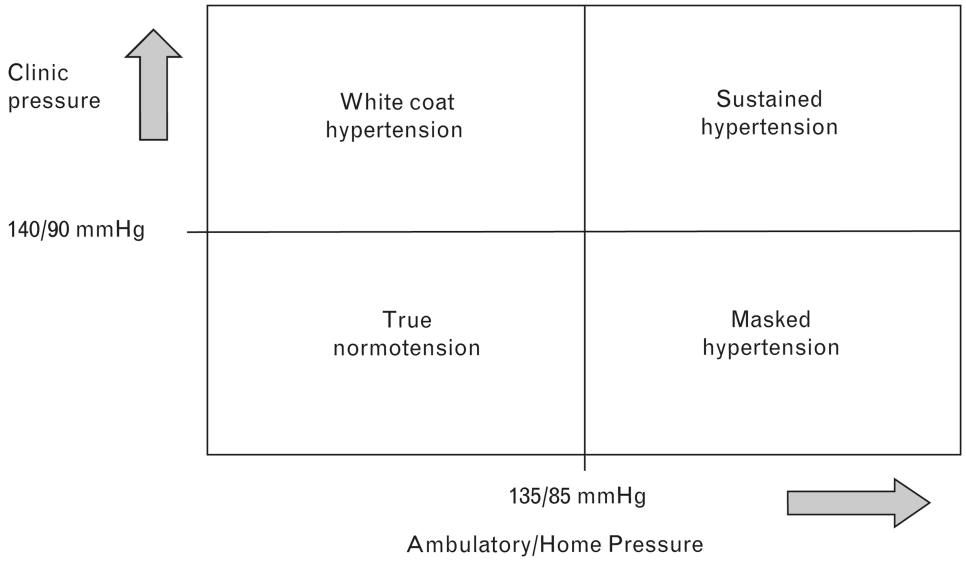

Fig. 2.
Classification of blood pressure status.

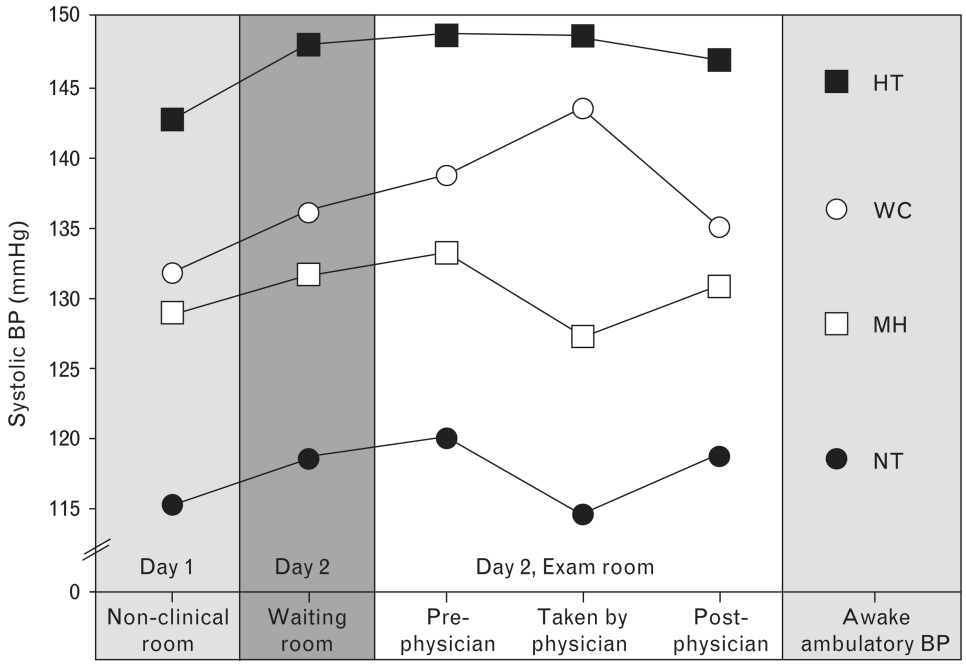

Fig. 3.

Measurement of clinic–ambulatory blood pressure differences. BP, blood pressure; HT, sustained hypertension; MH, masked hypertension; NT, true normotension; WC, white coat hypertension.

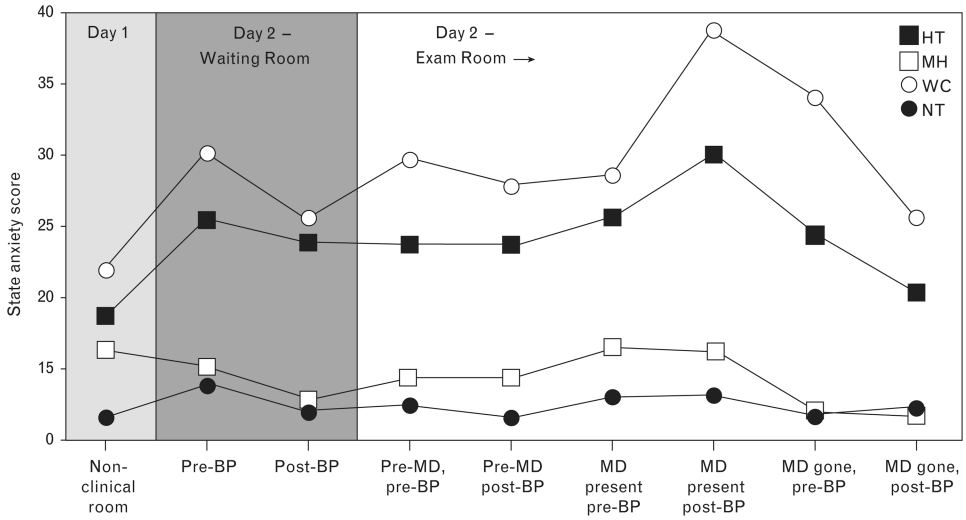

Fig. 4.

Blood pressure status and self-rated anxiety during physician measurement. BP, blood pressure; HT, sustained hypertension; MH, masked hypertension; MD, physician; NT, true normotension; WC, white coat hypertension.

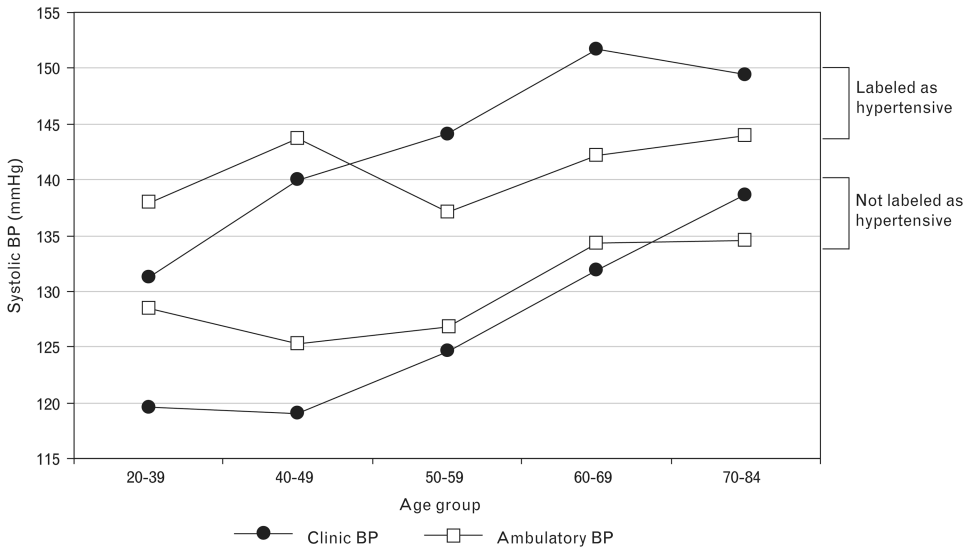

Fig. 5.

Relationships of clinic and ambulatory blood pressure with age in people who have been previously told (labeled) or not told (not labeled) that they have hypertension. BP, blood pressure.