Blood Pressure Monitoring Outside the Office for the Evaluation of Patients with Resistant Hypertension

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SUMMARY Although severe hypertension is associated with a poor prognosis, there exists a substantial number of patients who have persistently elevated blood pressures, but no signs of target organ damage, and nearly normal life expectancy. In such cases, measurement of blood pressure outside the clinic may give readings that are as much as 30 mm Hg lower than the clinic readings. The first step recommended in the identification of such patients is to use home blood pressure monitoring. If home blood pressures are low, 24-hour ambulatory blood pressure recording is indicated. If this also gives low readings, it is appropriate to treat patients according to their level of home blood pressure. Because of the unreliability of clinic pressures, ambulatory and home blood pressure monitoring may also be of value in assessing the response to treatment.

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Although it is well established that severe hypertension is associated with a poor prognosis, there is a substantial number of patients with persistently elevated office blood pressures who have no target organ damage and who have a near-normal life expectancy. This was documented in a number of studies conducted in the days before effective antihypertensive therapy became available. Thus, Perera reported that the average life expectancy for patients with systolic pressures greater than 200 mm Hg or diastolics greater than 120 mm Hg was 9 years. He wrote, “neither the initial level nor the maintained height of the casual blood pressure of those first observed in the uncomplicated phase showed any correlation with symptoms, rate of progression, or subsequent development of hypertension. This was not true, however, of patients with fixed high diastolic levels that remained elevated following rest or sedation; such patients varied greatly in their symptomatology, but with individual exceptions tended to develop complications more rapidly.” In another study, Burgess followed 100 patients who had pressures of at least 180/100 mm Hg during the previous 8 years, but no target organ damage, and reported that their life expectancy was nearly normal.

One explanation for these findings may be that hypertension is a heterogeneous process and that the prognosis depends on factors other than the height of the blood pressure; another is that there may be some patients in whom office pressures overestimate the height of blood pressure. That this can occur has been demonstrated in two studies comparing office and ambulatory pressures. In the first, by Littler et al., eight treated hypertensive patients who had persistently elevated clinic pressures but no target organ damage were compared with eight unselected untreated patients. In the former group, the average clinic pressures were 191/114 mm Hg, but the 24-hour pressures were only 172/83 mm Hg. In the latter, the difference between the two measures of pressure was much smaller (171/100 and 165/88 mm Hg). In the second study, by Floras et al., a group of hypertensive patients was identified whose clinic pressure exceeded their 24-hour ambulatory pressures by at least 10 mm Hg and was compared with another group who had similarly elevated clinic pressures but also elevation of 24-hour pressure. Target organ damage was much more pronounced in the group with high 24-hour pressures than in the group who had only high clinic pressures, being present in 64% of the former and 19% of the latter. This discrepancy between pressures measured in and outside the office has in fact been known for many years. In 1940, Ayman and Goldshine described comparisons of pressures taken in the office with pressures taken by the patients at home: 30% of their cases had office systolic pressures that were 40 mm Hg or more.

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greater than home systolic pressures. Mancia et al.\textsuperscript{6} used continuous intra-arterial blood pressure recording to demonstrate that the act of a physician putting on a blood pressure cuff and taking a reading could elevate the blood pressure by as much as 75/38 mm Hg. This phenomenon is less pronounced when a nurse takes the blood pressure, but it does not necessarily habituate with repeated visits. We have used the term "white coat hypertension" to describe this phenomenon.\textsuperscript{7}

Factors Responsible for the White Coat Effect

Despite the long-standing recognition of the existence of the white coat effect, the factors responsible for it are poorly understood. The most obvious explanation is that it is due to anxiety associated with an unfamiliar and threatening situation, producing the classic defense reaction. This explanation is unsatisfactory, however, because the defense reaction habituates with repeated exposure, and this does not necessarily occur with the white coat effect. It is our clinical impression that such patients are not generally characterized by a high level of anxiety.

It is generally more pronounced when a physician rather than a nurse takes the blood pressure. It may occur in patients with both mild and apparently severe hypertension, although we have found it to be more characteristic of the former.\textsuperscript{8} It may be greater in older than younger patients\textsuperscript{9} and is more common in women than in men.\textsuperscript{7} It does not appear to be related to baroreflex sensitivity (a determinant of general blood pressure variability) nor to blood pressure reactivity to other forms of mental stress such as mental arithmetic.\textsuperscript{4}

An alternative explanation is that it is a conditioned response. It is possible that in some subjects the clinic pressure is initially high because of anxiety and the defense reflex. By being informed that pressure is high and needs to be rechecked, the pressor response is reinforced at the next visit and becomes a chronic response. If this is specific to the encounter with the physician, it does not necessarily follow that the blood pressure is elevated at other times.

Assessment of the Response to Treatment

The success or failure of antihypertensive treatment is usually judged on the basis of blood pressure readings made in the physician's office. Resistant hypertension is, therefore, defined as persistence of markedly elevated office blood pressure readings after normally adequate doses of medication have been prescribed. While this phenomenon may have many causes, including a lack of patient compliance with medication, it has been suspected for many years that in some patients the continued high pressures may be attributed to "office hypertension" or an exaggerated white coat effect.\textsuperscript{10} In 1977, Ibrahim et al.\textsuperscript{11} investigated this possibility in 50 hypertensive patients who were evaluated by both office and home blood pressures. In the majority of patients, the two measures changed in parallel, but there were some patients in whom blood pressure control was judged to be poor by the clinic measurements but adequate by the home measurements. The effects of antihypertensive therapy were also analyzed by the regression of left ventricular hypertrophy in the electrocardiogram, and it was found that the changes in office blood pressures correlated less well with this than did home pressures. The authors concluded that "casual office readings may lead to misjudgment of the effectiveness of antihypertensive therapy."

Home blood pressure measurements have been shown to reflect the effects of antihypertensive medication on blood pressure.\textsuperscript{11-13} It is possible, however, that patients may not always be wholly objective in their reports of home blood pressures, as has been found to be the case with self-monitoring of blood glucose. Mazze et al.\textsuperscript{14} inserted a memory device in the home glucose monitors of a series of diabetic patients without the patients' knowledge and found that some patients consistently reported values lower than the true values. They concluded, "We identified a degree of unreliability and inaccuracy among the study subjects that would have a profound effect on the usefulness of patient-generated data." One practical solution to this dilemma is to use home blood pressure monitors that print out the data, thereby making falsification impossible.

A large number of studies investigating the use of ambulatory monitoring for evaluating the effects of antihypertensive medications has been published. For the most part, such studies have only reported the effects on 24-hour blood pressure and the duration of action of the drugs. Thus, Floras et al.,\textsuperscript{13} using invasive blood pressure monitoring, showed that when given in once-daily doses, pindolol lowered blood pressure for 15 hours, and atenolol for 24 hours. When judged by office pressures, one cause of apparent resistance to antihypertensive medication could thus be that the effects of the last dose of medication had worn off by the time the blood pressure was taken. Most such studies have not investigated whether there are any discrepancies between office and 24-hour pressures during antihypertensive treatment. Studies of \(\beta\)-blockers have shown that blood pressure variability is not affected,\textsuperscript{16} suggesting that reactivity to pressor stimuli is not necessarily reduced. One study by Gould et al.\textsuperscript{17} compared the blood pressure response to placebo and an \(\alpha\)-blocker (indoramin) using both clinic and ambulatory pressures for the evaluation. The placebo lowered clinic pressures by 15/10 mm Hg but had no effect on 24-hour pressures; the indoramin lowered clinic blood pressure by 18/13 mm Hg. These findings suggest that the placebo response is confined to the clinic and may in fact represent nothing more than dampening of the pressor response to the physician.

They also suggest that clinic measurements may underestimate the effects of antihypertensive medications. Rion et al.\textsuperscript{18} found that the response to antihypertensive medication was more reproducible when evaluated by ambulatory monitoring than by clinic pressures. Berglund et al.\textsuperscript{19} showed that a dose-response relationship for a new \(\beta\)-blocker (pafenolol)
could be obtained using 24-hour blood pressure but not with casual blood pressures.

**Current Status of Ambulatory Blood Pressure Monitoring**

There are now several commercially available non-invasive ambulatory blood pressure monitors that have received extensive validation testing. In general, these devices give reasonably accurate estimates of blood pressure, given the inherent limitations of the Korotkoff sound method, which they mostly use.²⁰

As a general rule, their inaccuracy is small when compared with the often large discrepancy between clinic pressures and average 24-hour pressures, which is one of the justifications for their use. They do not work well on all patients, and each recorder must be calibrated with each patient at the start of a recording. In addition, a certain amount of editing is needed to remove artifactual readings associated with movement.

These recordings show that the average 24-hour blood pressure is generally lower than the clinic pressure. The correlation between the two is about 0.6 to 0.7, which means that in some people there is a large discrepancy between them.²¹ We have investigated how many patients with elevated clinic pressures have normal 24-hour pressures. This was done by comparing 24-hour pressures in patients with different levels of clinic pressure with the 24-hour pressure of clinically normotensive subjects. Approximately 20% of patients with mild hypertension had normal 24-hour pressures, whereas less than 10% of patients with diastolic pressures above 105 mm Hg did.¹ This suggests that the number of patients who apparently have resistant hypertension, but really have white coat hypertension, is quite small.

For the majority of people, a normal day can be divided into three parts—working, being home, and sleeping. Blood pressure tends to be highest while at work, intermediate while at home, and lowest while sleeping.²⁰ The possible importance of the higher pressures during work is shown by the finding that the correlation between 24-hour blood pressure and left ventricular hypertrophy is strongest if the pressure is measured on a working as opposed to a nonworking day.²² The increased pressure at work has been attributed to psychosocial stress rather than to physical exertion. It could be argued that the elevation of pressure that occurs in the physician’s office reflects that individual’s response to stress and that clinic pressures are valid because they include this component. This is not necessarily the case, however, because there are many individuals who show an increased pressure in the clinic but not at work or during other periods of a normal day.

The main justification for reliance on the 24-hour pressures is that they have been consistently found to be more closely associated with target organ damage than clinic pressures. This was shown originally using a combination of fundal, chest x-ray, and electrocardiogram indices of target organ damage,²³ and more recently by studies using echocardiographically determined left ventricular hypertrophy.²⁴ There is also suggestive evidence from two studies that ambulatory blood pressures may give a better prediction of future cardiovascular morbid events than clinic pressures.²⁵ ²⁶

**Current Status of Home Blood Pressure Monitoring**

Home blood pressure monitoring has been available for much longer than ambulatory blood pressure monitoring but has been studied surprisingly little. It has the advantages of being inexpensive and convenient and can easily be managed by the majority of patients. As discussed previously, home pressures are nearly always lower than clinic pressures. It is not known, however, whether home pressures predict target organ damage or morbidity as well as or better than clinic pressures. We compared home and clinic pressures to 24-hour pressures in 93 patients and found that the correlation was somewhat closer using home pressures.²⁷ Recently another study has also reported that home blood pressures correlate more closely than clinic pressures with left ventricular hypertrophy.²⁸ Furthermore, the home pressures were more closely correlated with the degree of left ventricular hypertrophy than the clinic pressures. These findings are consistent with the earlier study of Ibrahim et al.¹ showing that regression of left ventricular hypertrophy with treatment was more closely related to home than to clinic pressure, but more data are needed on this point.

Another potential advantage of using home blood pressures is that they have been reported to improve patient compliance.²⁹ ³⁰ This may be particularly valuable in patients with hypertension that appears to be resistant to treatment but is, in fact, due to poor compliance.

There are now many electronic machines available that provide digital readings of blood pressure without the use of a stethoscope. We have evaluated 11 of these by comparing them with pressure determined simultaneously on the other arm with a mercury sphygmomanometer and stethoscope, and we found that only four machines gave readings that were consistently within 5 mm Hg of the mercury readings.³¹ In addition, the errors were consistently greater in patients with higher pressures. Such machines should, therefore, be used only when checked on each patient individually.

**Rationale for Blood Pressure Measurement Outside the Office in Patients with Resistant Hypertension**

A proposed schema for the evaluation of patients with apparently resistant hypertension is shown in Figure 1. By definition, such patients will have persistently elevated clinic blood pressures after several clinic visits despite being given appropriate treatment.

Evaluation of target organ damage should be carried out in all such patients. At the present time, the most sensitive test is the echocardiogram, which can detect left ventricular hypertrophy in a much greater number...
EVALUATION OF "RESISTANT" HYPERTENSION
BY AMBULATORY AND HOME BP MONITORING

Persistently elevated clinic BP

Target Organ Damage?

Yes

No

Home BP

High

Aggressive Treatment

Low

24 hr Ambulatory BP

High

Low

Treat according to home BP

FIGURE 1. Proposed schema of blood pressure measurement for patients with apparently resistant hypertension.

of patients than either the electrocardiogram or chest x-ray. The presence of left ventricular hypertrophy on the echocardiogram has recently been shown to be a potent predictor of morbidity that is independent of clinic pressures so that its presence warrants a definite indication for aggressive treatment.

The finding of persistently elevated clinic pressures without any left ventricular hypertrophy raises the possibility that the clinic pressure may be unrepresentative of pressures occurring at other times, as reported by Littler et al. In such patients, measurements of blood pressure outside the clinic is warranted. This can be done by either home blood pressure measurement or ambulatory monitoring. In fact, in all patients with resistant hypertension, a good case can be made for using home blood pressures on the grounds that the complex and changing treatment regimens that such patients are likely to be placed on will necessitate repeated evaluation of their blood pressures. With the use of home blood pressure monitoring, the dosages of medications may be more efficiently regulated, and the frequency of clinic visits may be curtailed.

In patients who have high clinic pressures but low home pressures, there is a therapeutic dilemma because of the relative paucity of information relating to the prognostic associated with a particular level of home blood pressure. If it is accepted that the prevailing or average level of pressure determines prognosis, rather than the peaks or troughs, it is important to know whether the clinic or home pressures are closer to the average level. This can best be determined by ambulatory monitoring, which is, therefore, appropriate when there is a large discrepancy between clinic and home pressures. If this shows that the average daytime pressure is closer to the home pressure than to the clinic pressure, relying on the home pressures to monitor the effects of treatment may be more appropriate than relying on the clinic pressure.

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