

Predictive value of ambulatory blood pressure shortly after withdrawal of antihypertensive drugs in primary care patients

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Abstract

Objective—To determine whether ambulatory blood pressure eight weeks after withdrawal of antihypertensive medication is a more sensitive measure than seated blood pressure to predict blood pressure in the long term.

Design—Patients with previously untreated diastolic hypertension were treated with antihypertensive drugs for one year; these were withdrawn in patients with well controlled blood pressure, who were then followed for one year.

Setting—Primary care.

Subjects—29 patients fulfilling the criteria for withdrawal of antihypertensive drugs.

Main outcome measures—Sensitivity, specificity, and positive and negative predictive value of seated and ambulatory blood pressure eight weeks after withdrawal of antihypertensive drugs.

Results—Eight weeks after withdrawal of medication, mean diastolic blood pressure returned to the pretreatment level on ambulatory measurements but not on seated measurements. One year after withdrawal of medication, mean diastolic blood pressure had returned to the pretreatment level both for seated and ambulatory blood pressure. For ambulatory blood pressure, the sensitivity and the positive predictive value eight weeks after withdrawal of medication were superior to those for seated blood pressure; specificity and negative predictive value were comparable for both types of measurement. Receiver operating characteristic curves showed that the results were not dependent on the cut off values that were used.

Conclusion—Ambulatory blood pressure eight weeks after withdrawal of antihypertensive drugs predicts long term blood pressure better than measurements made when the patient is seated.

Introduction

In hypertensive patients, antihypertensive drugs are usually given for an undetermined period of time. In patients with well controlled blood pressure, withdrawal of medication can be considered, particularly in those patients who comply with non-pharmacological recommendations or who suffer from side effects of the drugs that affect their quality of life.^{1,2} Fletcher *et al* reviewed case reports and randomised trials and found that success of withdrawal, defined as the proportion of patients remaining normotensive after withdrawal of medication, varied from 15% to over 50%.¹ However, it takes at least six to 12 months of follow up before a steady state has been reached because blood pressure may increase slowly after withdrawal of medication.

An indicator of likely return to raised blood pressure in an early phase after withdrawal of medication would be desirable. Ambulatory blood pressure monitoring

might be helpful in this regard. The reproducibility of ambulatory blood pressure is superior to that of seated blood pressure.³ To determine whether ambulatory blood pressure measured soon after stopping antihypertensive drugs is a more sensitive measure than seated blood pressure to predict blood pressure in the long term, we followed primary care patients who fulfilled the criteria for withdrawal of antihypertensive drugs for one year after withdrawal of medication.

Methods

A total of 145 patients (59% men) with untreated diastolic hypertension (four measurements ≥ 95 mm Hg on three occasions) aged between 25 and 75 years were included in an one year trial of treatment. Patients were randomised to treatment with amlodipine 5 mg or lisinopril 10 mg. Seated blood pressure was measured before and 4, 6, 12, 26, 39, and 52 weeks after the start of antihypertensive drugs. The therapeutic response was defined as a reduction in the average diastolic blood pressure (measured while the patient was seated) to a value of ≤ 90 mm Hg or as a fall from baseline of at least 10 mm Hg to a value of ≤ 100 mm Hg. For patients who did not meet the therapeutic response criterion after four weeks, the dosage was doubled. After one year of treatment, 122 patients receiving drug treatment completed the study. Reasons for not completing the study were: no therapeutic response after 12 weeks of treatment (two patients), withdrawal of informed consent (nine), hypotension (one), adverse events (nine), and angina pectoris (two). Ambulatory blood pressure was measured before and one year after the start of antihypertensive drugs (weeks 0 and 52).

WITHDRAWAL OF ANTIHYPERTENSIVE DRUGS

After one year of treatment, antihypertensive drugs were withdrawn in those patients whose diastolic blood pressure was below 90 mm Hg on all five measurements from week 6 until week 52 or whose average diastolic blood pressure was below 85 mm Hg. Seated and ambulatory blood pressure were measured eight weeks and one year after withdrawal of medication (weeks 60 and 104). Patients visited their general practitioner for blood pressure control during follow up; treatment was restarted if necessary.

EXAMINATIONS

Blood pressure was measured under controlled circumstances in the general practitioner's surgery. Seated blood pressure was measured in the right arm in the sitting position after five minutes of rest. Systolic and diastolic blood pressures were recorded at Korotkoff phase I and V at the nearest 2 mm Hg. During each visit, seated blood pressure was measured twice and the mean of these measurements was used.

Ambulatory blood pressure measured with Space-Labs 90207 equipment (Redmond, WA, USA). The

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Table 1—Mean (SE) seated and 24 hour ambulatory blood pressure (mm Hg) before the start of treatment (week 0), after one year of treatment (week 52), and eight and 52 weeks after withdrawal of medication (weeks 60 and 104)

	Week 0	Week 52	Week 60	Week 104
Seated blood pressure (n = 25)				
Systolic pressure	147 (3)	136 (3)	141 (3)	145 (4)
Diastolic pressure	95 (2)	85 (2)*	86 (1)*	91 (2)
24 Hour ambulatory blood pressure (n = 23)				
Systolic pressure	129 (3)	119 (2)**	129 (2)	131 (2)
Diastolic pressure	82 (1)	75 (1)**	82 (1)	84 (1)

*P<0.0005 for difference from value at weeks 0 and 104.

**P<0.0005 for difference from value at weeks 0, 52, and 104).

non-dominant arm was used unless a difference in seated blood pressure between arms had been found, in which case the arm with the highest blood pressure was used. A cuff size suitable for the arm circumference was selected. Ambulatory recordings were made only during weekdays when the patient was at work. Ambulatory blood pressure was recorded every 30 minutes during the day (7 00 to 22 59) and every 60 minutes during the night (23 00 to 6 59). Patients were instructed to keep the arm still at the time of measurement and to carry out normal activities during the 24 hours of measurement. When patients were receiving treatment, ambulatory measurements started 30-60 minutes before they took their drug and patients should not have missed any scheduled dose in the 24 hours before blood pressure measurements (measurements were repeated later if they had). Ambulatory blood pressure was analysed from raw data. The mean time-weighted blood pressure during 24 hours was calculated⁴ using reference values for normal 24 hour systolic ambulatory blood pressure of <135 mm Hg and diastolic ambulatory blood pressure of <85 mm Hg.^{5,6}

DATA ANALYSIS

Differences in blood pressure were tested using paired *t* tests. Sensitivity, specificity, and the positive and negative predictive value were calculated. Receiver operating characteristic curves were made for seated and ambulatory measurements. These curves represent the relation between corresponding values of sensitivity and specificity using different cut off points of blood pressure at week 60 to predict normal or raised blood pressure at week 104. To obtain a continuous curve (curve fitting), the functional form of the curve was assumed to be "binormal" and a modified Dorfman program was used to obtain maximum likelihood estimates of the curve.^{7,8} Areas under the curves were calculated.

Results

Thirty four of the 122 patients who completed the first year of treatment fulfilled the criteria for withdrawal of antihypertensive drugs. Twenty nine of these 34 patients agreed to participate in the follow up study. Their mean age was 51 (SE 2) years; 18 (63%) were male; mean body mass index (kg/m²) was 26.3 (0.6). After one year of follow up, data from 25 patients could be analysed for seated measurements and from 23 for ambulatory measurements. Reasons for not completing the study were: restart of antihypertensive drugs because of side effects of stopping (one patient) or increase in blood pressure (one); withdrawal of informed consent (two); refusal of remeasurement of ambulatory blood pressure after one year (two).

After eight weeks without antihypertensive drugs, mean diastolic blood pressure increased to the pretreat-

Table 2—Number of patients with normal or raised 24 hour ambulatory diastolic blood pressure at weeks 60 and 104 (eight and 52 weeks after withdrawal of medication)

Week 60	Week 104	
	≥85 mm Hg	<85 mm Hg
≥85 mm Hg	6	0
<85 mm Hg	3	14

Table 3—Number of patients with normal or raised seated diastolic blood pressure at weeks 60 and 104 (eight and 52 weeks after withdrawal of medication)

Week 60	Week 104	
	≥95 mm Hg	<95 mm Hg
≥95 mm Hg	0	1
<95 mm Hg	5	19

ment level for ambulatory measurements whereas mean diastolic blood pressure for seated measurements did not change (table 1). After 52 weeks without antihypertensive drugs, mean diastolic blood pressure returned to the pretreatment level for both seated and ambulatory measurements. No differences in mean systolic blood pressure were found for seated measurements. The mean systolic blood pressure for ambulatory measurements was significantly lower after 52 weeks of treatment than at weeks 0, 60, and 104.

Six of the nine patients with raised ambulatory blood pressure at week 104 were already hypertensive at week 60 (table 2); sensitivity was thus 66%. All 14 patients with normal ambulatory pressure at week 104 had a normal pressure at week 60 (specificity 100%). The positive and negative predictive values were 100% and 82%, respectively. Table 3 shows that none of the five patients with raised seated blood pressure at week 104 were hypertensive at week 60 (sensitivity 0%). Nineteen of the 20 patients with normal seated blood pressure at week 104 had normal pressure at week 60 (specificity 95%). The positive and negative predictive values were 0% and 79%, respectively.

Receiver operating characteristic curves for seated and ambulatory blood pressure show that the better prediction with ambulatory blood pressure than with seated blood pressure was not dependent on the cut off

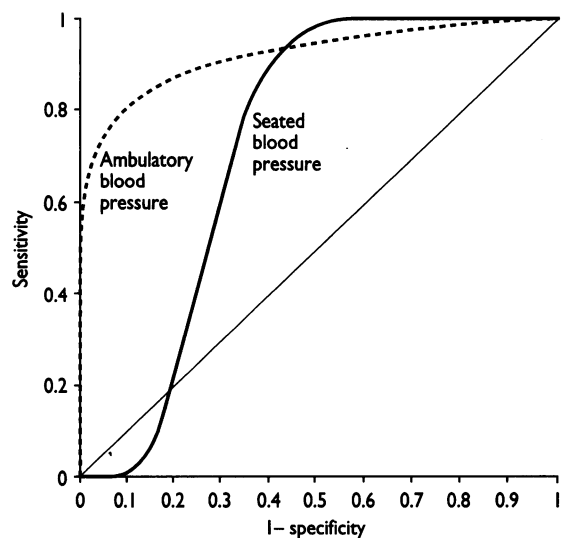


Fig 1—Receiver operating characteristic curves for seated and ambulatory blood pressure

value that was used (fig 1). The power of ambulatory measurements after eight weeks of withdrawal to predict ambulatory blood pressure after one year of withdrawal was large: the area under the curve was 0.92. The S shape of the curve for seated measurements was caused by a false positive case having the highest seated blood pressure at week 60 (see table 3). The area under the curve was 0.72.

Discussion

This study shows that ambulatory blood pressure measured eight weeks after withdrawal of antihypertensive drugs was more sensitive than seated blood pressure for predicting blood pressure in the long term. The sensitivity and the positive predictive value were superior for ambulatory measurements, and the specificity and negative predictive value were comparable for both types of measurements. Most patients with raised ambulatory blood pressure in the long term could be identified eight weeks after withdrawal of medication. Therefore, restarting of antihypertensive drugs in this early phase would have been justified on the basis of early ambulatory blood pressure monitoring.

The incidence of raised seated blood pressure eight weeks after withdrawal of medication was low, occurring in only two patients. One year after withdrawal of medication, one of these patients seemed normotensive and the other was excluded from the analysis because antihypertensive drugs were restarted. This low incidence of raised seated blood pressure, together with the relatively small number of patients, explains the very low sensitivity and positive predictive value of seated blood pressure found in this study. It is unlikely, however, that the large differences in area under receiver operating characteristic curves can be explained by the results in these patients. It is also unlikely that the superior predictive value of the ambulatory blood pressure after withdrawal of medication is dependent on regression to the mean. Since blood pressure was normal at all five visits during a period of 46 weeks, it is reasonable to assume that a steady state was reached.

It is well known that ambulatory blood pressure monitoring is a useful tool in a research setting. The method of recording of the blood pressure is more objective than for measurements in clinics or surgeries. Since mean blood pressure returned to the pretreatment level for ambulatory measurements, the results of this study suggest that seated measurements after withdrawal of medication are subject to a kind of placebo effect. Moreover, the relatively rapid return to pretreatment levels suggests that treatment in these patients

Key messages

- Seated blood pressure measured shortly after withdrawal of antihypertensive drugs is known to be an insensitive predictor for blood pressure in the long term
- Ambulatory measurements showed that the mean blood pressure returned to the pretreatment level within eight weeks after withdrawal of medication
- Eight weeks after drugs were withdrawn, ambulatory blood pressure was a good predictor of blood pressure in the long term, whereas seated blood pressure was not
- Restarting antihypertensive drugs at this time would be justified on the basis of early ambulatory blood pressure monitoring

with mild hypertension did not result in structural changes which influence the blood pressure.

No other studies have evaluated ambulatory blood pressure after withdrawal of antihypertensive medication. The present study shows that ambulatory blood pressure measured eight weeks after withdrawal of antihypertensive medication is more sensitive for predicting blood pressure in the long term than is seated blood pressure. These results should be confirmed by a double blind, placebo controlled study.

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ONE HUNDRED YEARS AGO

FEMININE CRUELTY.

It is a piece of almost proverbial wisdom that women are more cruel than men, and certainly the callous barbarism displayed by ladies of fashion and their imitators during the present season will go far to confirm the belief. Last year it was said that they had bought their hats before they knew that the feathers in them involved the destruction—sometimes under circumstances of great cruelty—of beautiful races of birds. But the birds' feathers have reappeared this year, and the excuse now given is that the feathers are "not real". Sir W.H. Flower

has written a letter in which he disposes of this absurd subterfuge. The fact is that these ladies, who are "priding themselves on their humanity" are, as they would themselves say, "monsters of cruelty" responsible for the wounding and maiming of myriads of birds, and the starving to death of countless families of nestlings. More suffering is produced to supply the bonnets for one garden party than in all the physiological laboratories of the world.

(*BMJ* 1896;iii:34.)