Original Article

Relation of Pulsatility of Brachial Artery Pressure to Resistant Hypertension

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Few studies have examined predictors of resistant hypertension. The aim of this study was to observe the relationship between resistant hypertension and the pulsatility of the brachial artery pressure, which is characterized as pulse pressure/diastolic pressure (PP/DP) and is a simple index of aortic input impedance. We obtained home blood pressure (BP) measurements for 102 patients aged 40–75 years with either office systolic BP (SBP) ≥ 140 mmHg or office diastolic BP (DBP) ≥ 90 mmHg. Patients were given a single antihypertensive agent or left untreated during the 2-week baseline period. Thereafter, patients were treated with 1 to 3 antihypertensive drugs for 1 year with a goal of achieving a home BP of less than 135/85 mmHg. At follow-up, 72 patients were taking a single drug with good BP control, 21 were taking two drugs with good BP control, and 9 were taking three drugs with poor BP control. Although office SBP at baseline was similar among the three groups, home morning and evening SBP at baseline in the single drug group were lower than those of the two- or three-drug groups ($p < 0.01$). Although office PP/DP at baseline did not differ among the three groups, home morning and evening PP/DP at baseline were highest in the three-drug group ($p < 0.01$). In multivariate analysis, only mean home PP/DP at baseline was correlated with BP control. There is a correlation between the pulsatility of the brachial artery pressure and the degree of BP control. (*Hypertens Res* 2004; 27: 641–646)

Key Words: hypertension, pulse pressure, pulsatility index

Introduction

Over the past two decades, public awareness of hypertension appears to have increased (1, 2). Despite significant efforts in diagnosing and treating hypertension, however, blood pressure (BP) control remains largely inadequate worldwide. In recent studies, fewer than 30% of hypertensive patients in the USA, and only 6% of those in the UK had attained BP values $< 140/90$ mmHg (1, 3). In addition, recent clinical trials suggest that resistant hypertension is increasingly common (1). Few studies have examined predictors of reaching the recommended target BP levels and resistant hypertension.

When characteristic impedance increases or systemic arteries stiffen under conditions of fixed cardiac function and peripheral resistance, the pulse pressure (PP) increases and

diastolic pressure (DP) decreases. Because the absolute PP is affected by changes in DP, it should be normalized by reasonable methods. A previous study suggested the ratio of PP to DP (PP/DP) to quantify pulsatility as relative PP instead of the estimation of input impedance, which represents the systemic arterial function (4). Recently, PP has been shown to be an independent predictive factor for cardiovascular risk in different populations (5, 6). Moreover, a high PP/DP has been associated with an increased risk of coronary artery disease (7).

Measurement of BP outside the clinician's office may provide valuable information for evaluation of patients with hypertension and for monitoring the response to treatment (1). Self-measurement has four general advantages: 1) distinguishing "white-coat hypertension"; 2) assessing the response to antihypertensive medications; 3) improving patient adherence to treatment; and 4) potentially reducing costs (8).

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However, whether the goal of management of hypertension is office BP or home BP is unclear.

The object of the present work was to investigate the relationship between the pulsatility of the brachial artery pressure and BP control as assessed by self-monitoring at home.

Methods

Patients Selection

Males and females aged 40–75 years were included if essential hypertension defined by the current use of therapy with a single antihypertensive agent or in the absence of treatment, by either office systolic BP (SBP) ≥ 140 mmHg or office diastolic BP (DBP) ≥ 90 mmHg. All patients had the ability to perform an appropriate number of BP measurements at home. Patients with renal failure (serum creatinine ≥ 1.2 mg/dl) were excluded from this study. This study was approved by the institutional ethics committee and each patient provided their informed consent to participate.

BP Measurements

Office BP Measurement

Office BP was measured twice by nurses or physicians using a mercury sphygmomanometer with the patient seated after at least 2 min of rest. The mean of the measurements of two consecutive visits was used for the analysis. These measurements were performed at baseline and at follow-up.

Home BP Measurement

Physicians or nurses instructed the subjects on how to measure their own BP at home prior to measurement. Then, we checked whether they were able to measure their BP correctly. The patients were asked to measure their BP in the sitting position every morning before breakfast and after more than 2 min of rest, and to record these measurements every day (9). If subjects were taking antihypertensive drugs, BP was measured before taking medication. Patients were also asked to measure their BP every evening just before going to bed. For home BP measurements, semi-automatic digitized devices (Omron Life Science Co., Ltd., Tokyo, Japan) based on the oscillometric method and which generate a digital display of SBP, DBP, and pulse rate, were provided to each household. Before monitoring commenced, the accuracy of the device was checked against a mercury column to ensure that the difference was not greater than 5 mmHg.

Measurement of Hemodynamic Variables

Patients were included in the study only if they exhibited 28 valid home BP measurements—14 in the morning and 14 in the evening—for both the baseline and follow-up periods. The mean of the 14 measurements was used for the analysis, respectively. The PP was determined by subtracting the DBP

from the SBP. Pulsatility of the brachial artery pressure was characterized as PP/DP (4).

Analysis of Response

The baseline phase consisted of a 2-week period of evaluation with two office visits, one on the first and one on the last day. Demographic data, medical history of the patients, cardiovascular risk factors and antihypertensive treatments were recorded, as well as office BP and home BP levels. Patients with home DBP < 85 mmHg and home SBP < 135 mmHg were excluded from this study. Evaluation of the follow-up phase was performed 1 year after. Patients who exhibited the target BP twice in 1 month were accepted as responders at follow-up.

Treatment

Additional therapy and dose increments in seven further steps were prescribed to reach the target BP. Drugs were modified to achieve a home BP of less than 135/85 mmHg (1). 1) If the response to the initial drug choice was inadequate after reaching the full dose, we substituted an agent from another class. 2) If patients responded inadequately to the substituted agent, we added a second drug. 3) Dosage titration of the second drug was used. 4) When the use of two drugs in adequate doses also failed to achieve the BP goal, the second drug was exchanged for a drug in another class. 5) If patients continued to respond inadequately to the use of two drugs, we added a third drug. 6) Dosage titration of the third drug was used. 7) When the use of three drugs in adequate doses also failed to achieve the BP goal, the third drug was exchanged for a drug in another class. Thereafter, BP data collection was repeated during the follow-up phase. Drug compliance was confirmed on each office visit. Patients were divided into three groups according to the number of antihypertensive agents and the target goal achievement.

Statistical Analysis

Data were expressed as the mean $\pm$ SD (for normally distributed variables) or as a percentage (for categorical variables). Analysis of variance (ANOVA) was used for comparison of normally distributed continuous variables. Difference in frequency were tested by χ^2 analysis. Univariate logistic regression analysis was used to select the independent predictive factors for lack of BP control. Covariates examined included clinical characteristics (age, sex, body mass index [BMI], risk factors, and complications), antihypertensive treatment at baseline and at follow-up, office SBP and DBP at baseline, home SBP and DBP at baseline, office PP/DP at baseline, and home PP/DP at baseline. Univariate predictors of lack of BP control with a p value < 0.05 were entered into a multivariate logistic regression model with stepwise selection. Differences were considered statistically significant at a val-

Table 1. Clinical Characteristics

	Single drug (n = 72)	Two drugs (n = 21)	Three drugs without good control (n = 9)
Age (years)	66 ± 7	64 ± 10	72 ± 5*
Sex (male/female)	28/44	8/13	7/2
BMI (kg/m ²)	23.7 ± 2.9	24.3 ± 3.6	24.2 ± 2.1
Risk factors			
Hyperlipidemia	40 (56%)	10 (48%)	2 (22%)
Diabetes mellitus	15 (21%)	3 (14%)	0 (0%)
Smoking [†]	4 (6%)	7 (33%)	1 (11%)
Complications			
Angina pectoris	2	0	1
Myocardial infarction	1	0	0
Cerebral accident	1	0	0
Treatment at baseline			
No	19	2	1
Ca antagonists	42	16	8
ACE inhibitors	5	1	0
β-Blockers	2	2	0
α-Blockers	1	0	0
ARB	3	0	0
Diuretics	0	0	0
Treatment at follow-up			
Ca antagonists	56	15	8
ACE inhibitors	4	10	4
β-Blockers	3	3	2
α-Blockers	0	4	3
ARB	9	9	8
Diuretics	0	1	2

Values are expressed as mean ± SD or number (%) of patients. * $p < 0.01$ vs. single drug group and two-drug group. † $p = 0.001$. BMI, body mass index; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blockers.

ue of $p < 0.05$.

Results

Patients

Four patients were excluded due to non-valid home BP measurement. The final group consisted of 102 patients (43 men, 59 women) ranging in age from 40 to 75, with a mean age of 66 ± 8 years. Their general characteristics are shown in Table 1. Four patients had coronary heart disease. The median BMI was 23.9 kg/m^2 . A significant difference in age was observed among the three groups ($p < 0.01$). BMI, complications, and all risk factors except for smoking status were similar among the three groups.

Antihypertensive Treatments

At baseline, 22 patients had not been prescribed drugs for hypertension. Sixty-six of the 80 patients receiving antihypertensive treatment (83%) received calcium channel blockers. At follow-up, 72 patients were taking a single drug with

good BP control, 21 were taking two drugs with good BP control, and 9 were taking three drugs with poor BP control. The most common single-line treatment was calcium antagonists (78%), followed by angiotensin II receptor blockers (13%), angiotensin converting enzyme (ACE) inhibitors (6%), and β-blockers (4%). Among those receiving two drugs, the most common combination was a calcium antagonist and an ACE inhibitor (29%), and the second most common was a calcium antagonist and an angiotensin II receptor blocker (24%). Diuretic therapy revealed inadequate BP control in 3 patients in the three-drug group. No specific drug or drug combinations were associated with better BP response.

Control of Hypertension and Pulsatility Index

Although office SBP at baseline was similar among the three groups, home morning and evening SBP at baseline in the single-drug group were lower than those in the two-drug or three-drug groups ($p < 0.01$, Table 2). Home morning and evening DBP at baseline were higher in the two-drug group than in the single-drug group. Although office PP/DP at baseline did not differ among the three groups, home morn-

Table 2. Changes of Blood Pressure and PP/DP

	Single drug	Two drugs	Three drugs without good control
Blood pressure (mmHg)			
Office SBP at baseline	157 ± 13	157 ± 12	161 ± 8
Office DBP at baseline	87 ± 8	89 ± 8	88 ± 8
Home SBP at baseline			
Morning	142 ± 15	154 ± 15*	160 ± 13*
Evening	136 ± 15	147 ± 15*	150 ± 13*
Home DBP at baseline			
Morning	82 ± 9	91 ± 12*	85 ± 10
Evening	78 ± 9	86 ± 10*	79 ± 10
Office SBP at follow-up	135 ± 4	135 ± 4	144 ± 5 [†]
Office DBP at follow-up	81 ± 3	82 ± 3	84 ± 4 [†]
Home SBP at follow-up			
Morning	128 ± 7	129 ± 7	146 ± 11 [†]
Evening	124 ± 7	125 ± 8	143 ± 11 [†]
Home DBP at follow-up			
Morning	75 ± 6	77 ± 9	79 ± 5
Evening	72 ± 5	74 ± 6	77 ± 7 [†]
Heart rate (beats/min)			
At baseline	69 ± 8	68 ± 11	64 ± 8
At follow-up	68 ± 7	67 ± 9	66 ± 5
PP/DP at baseline			
Office	0.80 ± 0.14	0.77 ± 0.18	0.83 ± 0.14
Home (mean)	0.74 ± 0.16	0.72 ± 0.20	0.90 ± 0.17 [†]
Morning	0.73 ± 0.16	0.72 ± 0.19	0.90 ± 0.18 [†]
Evening	0.74 ± 0.16	0.72 ± 0.21	0.91 ± 0.17 [†]

Values are expressed as mean. * $p < 0.01$ vs. single drug group, [†] $p < 0.01$ vs. single drug group and two-drug group, [‡] $p < 0.05$ vs. single drug group. SBP, systolic blood pressure; DBP, diastolic blood pressure; PP/DP, pulse pressure/diastolic pressure. Heart rate: average of the morning heart rate and the evening heart rate.

Table 3. Univariate and Multivariate Regression Analysis for Blood Pressure Control

	Univariate <i>p</i>	Multivariate coefficient ± SD	<i>p</i> value
Diabetes mellitus	0.0233	—	—
Hyperlipidemia	0.0474	—	—
Mean home PP/DP at baseline	0.0008	0.99 ± 0.34	0.0001

PP/DP, pulse pressure/diastolic pressure.

ing and evening PP/DP at baseline were highest in the three-drug group ($p < 0.01$). Office SBP and DBP at follow-up, and home morning and evening SBP at follow-up, were also highest in the three-drug group ($p < 0.01$, respectively).

Logistic Regression Analysis

Univariate logistic regression analysis revealed that diabetes mellitus, hyperlipidemia, and mean home PP/DP at baseline were all significantly related to BP control (Table 3). Age, sex, BMI, smoking, treatment at baseline and at follow-up, and office and home BP at baseline were unrelated to the degree of BP control. In multivariate analysis, only a high val-

ue of mean home PP/DP at baseline was significantly correlated with a lack of BP control.

Discussion

Significance of Pulsatility of the Brachial Artery Pressure

BP is a periodic phenomenon that can divide into two components: a steady component and a pulsatile component. The pulsatile component is influenced by the changes in ventricular ejection, large artery compliance, and timing of reflected waves. Since arteriosclerosis decreases the compliance of the aortic artery, aortic input impedance increases in patients

with this disease. Although ascending aortic input impedance would be the clearest index of arteriosclerosis, there are no simple and non-invasive variables pertaining to the dynamic mechanical properties of the arterial system. A recent report suggests that the pulsatility of the brachial artery pressure is a simple tool to evaluate arterial input impedance (7). The input impedance depends not only on ventricular ejection but also on peripheral vascular resistance. Because, in older subjects, ventricular ejection is normal or even decreased, the main determinant of input impedance is increased peripheral vascular resistance. Therefore, the pulsatility of the brachial artery pressure reflects arterial input impedance, particularly peripheral vascular resistance.

A substantial body of evidence documents both the increased risks of cardiovascular diseases associated with hypertension and the benefits gained when BP is sufficiently reduced (10, 11). Despite the significant advances in diagnosing and treating hypertension, BP is normalized in less than one-third of hypertensive patients worldwide (12). This may be at least partly because factors predicting BP control have not been conclusively identified. In a previous work, for example, neither gender nor hypertension duration was linked to BP control (13). The results of this study demonstrate that patients with increased arterial input impedance are likely to have poor BP control. The pulsatility of brachial artery pressure may thus be a predictive factor for BP control.

Resistant Hypertension

Resistant hypertension has historically been defined as the failure of concomitant use of three of more different antihypertensive agents to lower BP to less than 140/90 mmHg (14). Several conditions, such as older age and obesity, have been associated with variable increases in BP that can impair responsiveness to medications (14). Cross-sectional studies have indicated that increasing BMI independently correlates with increasing number of prescribed antihypertensive medications (15). In the present study, because BMI was similar among the three groups, older age correlated with lack of BP control. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) trial indicated that poor SBP control more commonly determines therapeutic resistance, and that control of SBP worsens with age (16). In addition, after 1 year of treatment in the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial, 90% of subjects had their DBP reduced to the target value (<90 mmHg), but only 71% of subjects achieved the goal SBP (<140 mmHg) (17). Resistant hypertension is a consequence of the SBP remaining uncontrolled.

Poor adherence to prescribed antihypertensive agents and lack of access to medical care have also been considered as causes of uncontrolled hypertension (18, 19). Moreover, physicians' attitudes regarding antihypertensive therapy play a crucial role in adequate BP control (20). Home BP measurements are indispensable for the improvement of manage-

ment of hypertension in medical practice (9). Home BP measurements also improve drug compliance and patients' attitudes regarding access to medical care. Home BP measurements may provide an accurate estimation index of BP control during treatment. Possibly the most common physiologic cause for resistant hypertension is volume overload (21). A previous study reported that more than two-thirds of patients with resistant hypertension had elevated plasma volume (22). In resistant hypertensives, attention to sodium intake and basing the antihypertensive regimen on aggressive diuretic therapy may lead to success in reaching the goal BP. On the other hand, several patients were intolerant of diuretics (14). Diuretic therapy showed inappropriately BP control in this study. Two randomized, placebo-controlled trials on the use of combination therapy with diuretics and β -blockers for the treatment of uncontrolled hypertension reported that there were no statistically significant differences in the BP-lowering effects or tolerability among the various third-line agents (23, 24). Further carefully controlled clinical trials will be needed to determine the most cost-effective approach for improving BP control and reducing cardiovascular risk.

Study Limitations

There are potential limitations regarding the interpretation of these data. First, the relatively small number of patients eligible for analysis in this study may render it difficult to generalize the results and to apply them to other patient populations. In addition, we did not examine other causes of uncontrolled hypertension, such as dietary sodium ingestion and alcohol ingestion. Further studies are required to clarify the relationship between PP/DP and the effect of antihypertensive treatments. Second, treatment biases are possible. Different antihypertensive drugs may affect pulsatility to a different degree. When multivariate analysis was used in this study, the selections or combinations of antihypertensive drugs at baseline and at follow-up did not affect the achieving of target levels. Third, we used home BP measurements taken with semi-automatic digitized devices. A previous report has calculated PP/DP using office BP (7). Since the accuracy and reproducibility of PP/DP were important, in this study, the average of 14 measurements of home BP was used for calculation of PP/DP. The Japanese Society of Hypertension guidelines recommended that the measurements be averaged over 2 weeks for the evaluation of home BP (9).

In conclusion, the pulsatility of the brachial artery pressure may be a predictive factor for resistant hypertension.

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