Significance of Pulsatility of Brachial Artery Pressure for Blood Pressure Control

Yuji YOSHITOMI,[1] MD, Toshikazu ISHII,[2] MD, Takashi TSUJIBAYASHI,[3] MD, Masashi KANEKI,[4] MD, *and* Shun-ichiro SAKURAI,[5] MD

SUMMARY

Few studies have examined predictors of poor blood pressure (BP) control. The aim of this study was to observe the relationship between the pulsatility of brachial artery pressure characterized as pulse pressure/diastolic pressure (PP/DP), suggesting aortic input impedance, and poor BP control.

We obtained office BP measurements for 94 patients aged 40-75 years with either office systolic BP (SBP) ≧ 140 mmHg or diastolic BP (DBP) ≧ 90 mmHg. Patients were given a single antihypertensive agent or were untreated at baseline. The angiotensin II receptor blocker valsartan (80 mg) was administered to all patients. Patients were treated with 1 to 2 antihypertensive drugs (valsartan only or valsartan + Ca antagonist) for 6 months to achieve an office BP of less than 140/90 mmHg.

At follow-up, 32 patients were taking a single drug (valsartan) with good BP control, 24 were receiving two drugs with good BP control, and 38 were on two drugs with poor BP control. SBP and DBP at baseline were similar in the 3 groups. PP/DP at baseline differed in the 3 groups ($P < 0.01$). In multivariate analysis, only PP/DP at baseline correlated with lack of BP control.

The pulsatility of brachial artery pressure is associated with achieving adequate BP control. (Int Heart J 2008; 49: 295-302)

Key words: Angiotensin II receptor blocker, Pulsatility index, Pulse pressure

EPIDEMIOLOGIC studies have shown that people with high blood pressure (BP) are at greater risk for cardiovascular or cerebrovascular events.[1-4] The goal in the management of hypertension is to reduce the incidence of morbidity and mortality from cardiovascular events. Although the importance of reducing BP is well known, only one quarter of hypertensive patients are adequately controlled to a BP of 140/90 mmHg or less.[5] Fewer than 30% in the USA, and only 6% in the UK had attained BP values < 140/90 mmHg.[5,6] In addition, recent clinical trials suggest that resistant hypertension is increasingly common.[5] Therefore,

From [1] Miyauchi Makoto Memorial Clinic, [2] Ishii Medical Clinic, [3] Tsujibayashi Medical Clinic, [4] Kaneki Medical Clinic, and [5] Sakurai Medical Clinic, Shizuoka, Japan.

Address for correspondence: Yuji Yoshitomi, MD, Miyauchi Makoto Memorial Clinic, 9-44 Izumi-cho, Mishima, Shizuoka 411-0037, Japan.

Received for publication January 16, 2008.

Revised and accepted March 13, 2008.

despite the numerous drugs available for the treatment of hypertension, adequate control of high BP and hence, adequate protection against the risk of cardiovascular disease, has yet to be achieved in the vast majority of hypertensive patients.

When characteristic impedance increases or systemic arteries stiffen under conditions of fixed cardiac function and peripheral resistance, the pulse pressure increases and diastolic pressure decreases. Because the absolute pulse pressure is affected by changes in diastolic pressure, it should be normalized by reasonable methods. A previous study suggested the ratio of pulse pressure to diastolic pressure (PP/DP) to quantify pulsatility as relative pulse pressure instead of the estimation of input impedance, which represents the systemic arterial function.[7] Recently, pulse pressure is an independent predictive factor for cardiovascular risk in different populations.[8,9] Hatsuda, *et al* showed the correlation of pulse pressure and aortic stiffness.[10] Moreover, the PP/DP was associated with an increased risk of coronary artery disease.[11]

The object of the present work was to investigate the relationship between the pulsatility of brachial artery pressure and the attainment of target BP goals.

METHODS

Patient 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) $\geqq$ 140 mmHg or office diastolic BP (DBP) $\geqq$ 90 mmHg. Patients with renal failure (serum creatinine $\geqq$ 1.2 mg/dL) were excluded from the study. Each patient provided informed consent for this study.

BP measurements and measurement of hemodynamic variables: Office BP was measured by a nurse or physician twice consecutively with the patient seated, after at least 2 minutes of rest using a mercury sphygmomanometer. The mean of the measurements of two consecutive visits was considered for the analysis. These measurements were performed at baseline and at follow-up.

The pulse pressure (PP) was determined by subtracting the DBP from the SBP. Pulsatility of the brachial artery pressure was characterized as PP/DP.[7]

Analysis of response: The baseline phase consisted of a 2-week period of evaluation with two separate visits performed 2 weeks apart. Demographic data, medical history of the patients, cardiovascular risk factors and antihypertensive treatments were recorded as well as office BP levels. Evaluation of follow-up phase was performed after 6 months. Patients who exhibited the target BP twice for one month were assigned to the good BP control groups at follow-up.

Treatment: Drugs were modified to achieve office BP of less than 140/90 mmHg.[5] There was no wash-out period. Valsartan 80 mg was administered to the

no treatment patients, once daily in the morning. Patients already receiving valsartan continued the drug. If the response to the initial drug choice was inadequate, we added a second drug. A Ca antagonist was administered to patients receiving valsartan. We added valsartan 80 mg to patients receiving a Ca antagonist. Thereafter, BP data collection was repeated at follow-up phase. Drug compliance was confirmed every visit. Patients were divided into 3 groups according to the number of antihypertensive agents and the target goal achievement.

Statistical analysis: Data are expressed as the mean ± standard deviation (for normally distributed variables) and percentage (for categorical variables). Analysis of variance (ANOVA) was used to compare normally distributed continuous variables. Differences 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 and daily dose at baseline and at follow-up, SBP, DBP, mean blood pressure (MBP) and PP at baseline, and 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 value of $P < 0.05$.

RESULTS

Patients: The study patients consisted of 94 patients (33 men, 61 women), rang-

Table I. Clinical Characteristics

	Single drug (n = 32)	Two drugs (n = 24)	Two drugs with poor BP control (n = 38)
Age (years)	69 ± 14	69 ± 9	72 ± 12
Sex (M/F)	9/23	10/14	14/24
BMI (kg/m^2)	24.6 ± 4.0	23.9 ± 3.3	24.0 ± 3.0
Risk factors			
Hyperlipidemia	16 (50%)	7 (29%)	20 (53%)
Diabetes mellitus	6 (19%)	3 (13%)	7 (18%)
Smoking	4 (13%)	2 (8%)	1 (3%)
Complications			
Angina pectoris	2	1	1
Myocardial infarction	0	0	1
Cerebral accident	1	0	0
Treatment at baseline			
No	32	10	8
Ca antagonists	0	13	24
Valsartan	0	1	6

Values are expressed as mean ± SD or number (%) of patients. BMI indicates body mass index.

ing in age from 40 to 75, with a mean age of 70 ± 12 years. Their general characteristics are shown in Table I. Five patients had coronary heart disease. Median BMI was 24.0 kg/m^2, with the group median values ranging from 23.5 to 25.5 kg/m^2. Age, sex, BMI, risk factors, and complications were similar in the 3 groups.

Antihypertensive treatments: At baseline, 50 patients had not been prescribed drugs for hypertension. Thirty-seven of 44 patients with antihypertensive treatment (39%) received calcium channel blockers and 7 (7%) received valsartan. At follow-up, 32 patients were taking a single drug (valsartan) with good BP control, 24 were taking two drugs with good BP control, and 38 were taking two drugs with poor BP control. Specific drugs or drug combinations did not lead to better BP response.

Control of hypertension and pulsatility index: Mean BP was 156 ± 15/90 ± 10 mmHg at baseline. At follow-up, mean BP was 137 ± 9/81 ± 8 mmHg. SBP and DBP at baseline were similar in the 3 groups (Table II). PP/DP at baseline differed in the 3 groups ($P < 0.01$). At follow-up, SBP in the group receiving two drugs with poor BP control was the highest among the 3 groups ($P < 0.01$). DBP

Table II. Treatment and Changes in Blood Pressure and PP/DP

	Single drug	Two drugs	Two drugs with poor BP control
Blood pressure (mmHg)			
SBP at baseline	154 ± 6	153 ± 15	158 ± 19
DBP at baseline	91 ± 6	90 ± 9	89 ± 13
SBP at follow-up	131 ± 5	130 ± 6	145 ± 6*†
DBP at follow-up	80 ± 5	79 ± 5	82 ± 10
Heart rate (beats/min)			
At baseline	69 ± 8	70 ± 9	69 ± 8
At follow-up	68 ± 7	68 ± 8	71 ± 8
PP/DP at baseline	0.69 ± 0.13	0.70 ± 0.13	0.80 ± 0.25*†
PP/DP at follow-up	0.64 ± 0.10	0.66 ± 0.12	0.79 ± 0.26*†

Values are expressed as the mean ± SD.
* $P < 0.05$ versus single drug group, † $P < 0.05$ versus two drugs group.
SBP indicates systolic blood pressure; DBP, diastolic blood pressure; and PP/DP, pulse pressure/diastolic blood pressure.

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

	Univariate *P*	Multivariate coefficient ± standard error	*P*
PP at baseline	0.023	-	-
PP/DP at baseline	0.016	1.11 ± 0.45	0.0162

PP indicates pulse pressure and PP/DP, pulse pressure/diastolic blood pressure.

did not differ among the 3 groups.

Logistic regression analysis: Univariate logistic regression analysis, PP at baseline, and PP/DP at baseline were significant variables for lack of BP control (Table III). Age, BMI, smoking, antihypertensive treatment at baseline and at follow-up, and SBP, DBP, and MBP at baseline were unrelated to lack of BP control. In multivariate analysis, only PP/DP at baseline significantly correlated with lack of BP control.

DISCUSSION

Significance of pulsatility of brachial artery pressure: BP is a periodic phenomenon that can be divided 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 hypertensive patients. Although ascending aortic input impedance would be the clearest index of arteriosclerosis, there are no simple and noninvasive 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 with which to evaluate arterial input impedance.[11] The input impedance depends not only on ventricular ejection but also on peripheral vascular resistance. Since ventricular ejection is normal or even decreased in older subjects, the main determinant of input impedance in such conditions is increased peripheral vascular resistance. Therefore, the pulsatility of the brachial artery pressure reflects arterial input impedance, particularly peripheral vascular resistance.

Arterial stiffness of the central artery has been reported to be associated with the development of ischemic heart disease.[10,12] A substantial body of evidence has documented both the increased risks of cardiovascular diseases associated with hypertension and the benefits gained when BP is sufficiently reduced.[13,14] The identification of predictive factors of BP control is not conclusive. Neither gender nor hypertension duration was linked to BP control.[15] Increased PP appears to be the most powerful measure available to identify hypertensive patients at greater risk for subsequent myocardial infarction.[16,17] Ozaki, *et al* reported that aortic PP is correlated with coronary artery stenosis.[18] However, whether PP is associated with poor BP control is unclear. In addition, MBP rather than PP was related to lack of BP control.[19] The results of this study demonstrate that poor BP control is related to increased arterial input impedance. The pulsatility of brachial artery pressure, rather than PP and MBP, may be a predictive factor for BP control.

Ca antagonists lower BP by relaxing arteriolar smooth muscle and decreasing peripheral vascular resistance.[20] Angiotensin II increases total vascular resistance via direct and indirect effects on blood vessels. Angiotensin II receptor blockers (ARBs) lower total vascular resistance and MBP, SBP, and DBP in various hypertensive states.[21] Therefore, Ca antagonists may have an effect on PP/DP. Our data cannot address the relationship between antihypertensive drugs and PP/DP.

Uncontrolled hypertension: In clinical practice, the aims of antihypertensive therapy can be considered to be normal or optimal BP control, and the prevention of complications, without impairing quality of life. However, for a wide range of antihypertensive therapies, BP control remains poor in a majority of patients. In particular, systolic BP is generally poorly controlled in clinical practice. A previous report suggested that a diastolic BP below 90 mmHg was achieved in approximately 70% of patients, and relatively few had BP of 95 mmHg or above; by contrast, a systolic BP below 140 mmHg was achieved only in approximately 45%, and about 20% had a systolic BP of 160 mmHg or above.[22] Similarly, data from the Hypertension Optimal Treatment (HOT) study indicate that only 46% achieved the widely advocated target of 140 mmHg or below.[13] Such findings suggest that, although diastolic BP targets set out in management guidelines may be feasible, in practice systolic BP targets are often difficult to achieve.

In recent years, ARBs have become available for clinical practice and have been found to be superior to angiotensin converting enzyme (ACE) inhibitors for directly blocking the effects of angiotensin II. There is compelling evidence that ACE inhibitors reduce the risk of death and myocardial infarction in patients with heart failure, acute coronary syndromes, and coronary artery disease, as well as those in other high risk populations. ARBs have rapidly become established as one of the leading therapeutic classes in the management of hypertension. Due to their excellent safety profile and documented mechanism for organ protection, the clinical use of ARBs has become increasingly popular in patients with hypertension, heart failure, diabetic nephropathy, and other clinical conditions in Japan.[23] However, clinical trials comparing ARBs with placebo or active controls have failed to produce reductions in death and myocardial infarction.[24] Moreover, ARBs clearly have not amassed an equivalent database. The SCOPE trial showed that only 26% of patients who received candesartan alone achieved target BP levels.[25] Hypertension is a heterogeneous condition in which both genetic and environmental factors contribute to varying extents. Due to this heterogeneity, monotherapy with any antihypertensive agent is unlikely to control BP adequately in more than 50-60% of patients, even in mild-to-moderate hypertension.[26]

Poor adherence to prescribed hypertensive agents and lack of access to med-

ical care have been also considered as causes of uncontrolled hypertension.[27,28] It is clear that hypertension is not managed aggressively enough and that physicians are often conservative in their approach, not making alterations to therapy even if BP remains elevated. The problem of under-treatment may be exacerbated by the number and complexity of management guidelines, so that many doctors may be unfamiliar with recommended treatment strategies. Home BP measurements are indispensable for the improvement of management of hypertension in medical practice.[29] Moreover, home BP measurement also improves drug compliance and frequency of access to medical care. Home BP measurements may bring accurate assessment of BP control during treatment.

Study limitations: There are potential limitations regarding the interpretation of these data. First, the relatively small selected number of patients eligible for analysis in this study may render it difficult to generalize the results and 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 effect of antihypertensive treatments. Second, treatment biases are possible. Different antihypertensive drugs may affect pulsatility to a different degree. When multivariate analysis was used, the selections or combinations of antihypertensive drugs at baseline and at follow-up did not affect the attainment of target levels.

In conclusion, the pulsatility of the brachial artery pressure may be a predictive factor for poor BP control.

REFERENCES

1. MacMahon S, Peto R, Cutler J, *et al*. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet 1990; 335: 765-74.
2. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blockers vs diuretic: The Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002; 288: 2981-97.
3. Hansson L, Lindholm LH, Ekbom T, *et al*. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. Lancet 1999; 354: 1751-6.
4. Hozawa A, Ohkubo T, Kikuya M, *et al*. Blood pressure control assessed by home, ambulatory and conventional blood pressure measurements in the Japanese general population: the Ohasama study. Hypertens Res 2002; 25: 57-63.
5. The Sixth Report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Arch Intern Med 1997; 157: 2413-46.
6. Colhoun HM, Dong W, Poulter NR. Blood pressure screening, management and control in England: results from the health survey for England 1994. J Hypertens 1998; 16: 747-52.

7. Sunagawa K, Burkhoff D, Lim KO, Sagawa K. Impedance loading servo pump system for excised canine ventricle. Am J Physiol 1982; 243: H346-50.
8. Benetos A, Safar M, Rudnichi A, *et al*. Pulse pressure: a predictor of long-term cardiovascular mortality in a French male population. Hypertension 1997; 30: 1410-5.
9. Inoue T, Matsuoka M, Nagahama K, *et al*. Cardiovascular risk factors associated with pulse pressure in a screened cohort in Okinawa, Japan. Hypertens Res 2003; 26: 153-8.
10. Hatsuda S, Shoji T, Shinohara K, *et al*. Regional arterial stiffness associated with ischemic heart disease in type 2 diabetes mellitus. J Atheroscler Thromb 2006; 13: 114-21.
11. Yamashita N, Nakayama Y, Tsumura K, *et al*. Pulsatility of brachial artery pressure is associated with an increased risk of coronary artery disease in men. J Hypertens 2001; 19: 1589-93.
12. Benetos A, Safar M, Rudnichi A, *et al*. Pulse pressure: a predictor of long-term cardiovascular mortality in a French male population. Hypertension 1997; 30: 1410-5.
13. Hansson L, Zanchetti A, Carruthers SG, *et al*. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet 1998; 351: 1755-62.
14. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000; 342: 145-53.
15. Mallion JM, Genès N, Vaur L, *et al*. Blood pressure levels, risk factors and antihypertensive treatments: lessons from the SHEAF study. J Hum Hypertens 2001; 15: 841-8.
16. Madhavan S, Ooi WL, Cohen H, Alderman MH. Relation of pulse pressure and blood pressure reduction to the incidence of myocardial infarction. Hypertension 1994; 23: 395-401.
17. Benetos A, Zureik M, Morcet J, *et al*. A decrease in diastolic blood pressure combined with an increase in systolic blood pressure is associated with higher cardiovascular mortality in men. J Am Coll Cardiol 2000; 35: 673-80.
18. Ozaki M, Masuoka H, Kawasaki A, Ito M, Nakano T. Intraortic pulse pressure is correlated with coronary artery stenosis. Int Heart J 2005; 46: 69-78.
19. Yoshitomi Y, Nagakura C, Miyauchi A. Significance of mean blood pressure for blood pressure control. Int Heart J 2005; 46: 691-9.
20. Lehmann HU, Hochrein H, Witt E, Mies HW. Hemodynamic effects of calcium antagonists. Hypertension 1983; 5: II66-73. (Review)
21. Oates JA. Antihypertensive agents and the drug therapy of hypertension. In: Hardman JG, Limbird LE, Gilman AG, et al eds. *The Pharmacological Basis of Therapeutics*. 9th ed. New York: McGraw-Hill, 1996; 780-808.
22. Perry HM Jr, Bingham S, Horney A, *et al*. Antihypertensive efficacy of treatment regimens used in Veterans Administration hypertension clinics. Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. Hypertension 1998; 31: 771-9.
23. Wong J, Patel RA, Kowey PR. The clinical use of angiotensin-converting enzyme inhibitors. Prog Cardiovasc Dis 2004; 47: 116-30. (Review)
24. Epstein BJ, Gums JG. Angiotensin receptor blockers versus ACE inhibitors: prevention of death and myocardial infarction in high-risk populations. Ann Pharmacother 2005; 39: 470-80. (Review)
25. Lithell H, Hansson L, Skoog I, *et al*; SCOPE Study Group. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. J Hypertens 2003; 21: 875-86.
26. Materson BJ, Reda DJ, Cushman WC. Department of veterans affairs single-drug therapy of hypertension study. Revised figures and new data. Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. Am J Hypertens 1995; 8: 189-92.
27. Shea S, Misra D, Ehrlich MH, Field L, Francis CK. Predisposing factors for severe, uncontrolled hypertension in an inner-city minority population. N Engl J Med 1992; 327: 776-81.
28. Knight EL, Bohn RL, Wang PS, Glynn RJ, Mogun H, Avorn J. Predictors of uncontrolled hypertension in ambulatory patients. Hypertension 2001; 38: 809-14.
29. Imai Y, Otsuka K, Kawano Y, *et al*; Japanese Society of Hypertension. Japanese society of hypertension (JSH) guidelines for self-monitoring of blood pressure at home. Hypertens Res 2003; 26: 771-82.