Original Article

Blood Pressure Is the Main Determinant of the Reflection Wave in Patients with Type 2 Diabetes

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Augmentation index (AI), the ratio of augmented pressure by the reflection pressure wave to the pulse pressure (PP), is an index of arterial stiffness and central blood pressure (BP). Although type 2 diabetes mellitus (DM) is a major risk factor for atherosclerosis, there is controversy with respect to how DM affects AI. In the present study, we investigated possible determinants of AI in 194 type 2 DM patients (mean age 67±9 years). AI was measured in the left radial artery using an automated tonometric method. In a simple correlation analysis, AI showed a positive association with age, and a negative association with body height, body weight, waist circumference, heart rate (HR), plasma glucose, and HbA1c. Women had significantly higher AI than men. Stepwise regression analysis revealed that mean BP (MBP) (β=0.260, p<0.001), HR (β=−0.550, p<0.001) and body height (β=−0.217, p<0.001) were independent determinants of radial AI. Similarly, the second peak of systolic BP (SBP2), an index of central aortic systolic BP (SBP), showed a positive association with age, BMI, waist circumference, MBP and AI, and a negative association with body height. In a separate analysis performed in diabetic patients with treated hypertension (n=123), again, only MBP, HR and body height were significant determinants of radial AI. There was no difference in radial AI and SBP2 among the classes of antihypertensive drugs used. These findings indicate that tight BP control would be effective in reducing the reflection wave and aortic BP, which could independently relate to cardiovascular disease in type 2 diabetic patients. (*Hypertens Res* 2008; 31: 493–499)

Key Words: **augmentation index (AI), arterial stiffness, diabetes mellitus**

Introduction

It has been demonstrated that hypertension is a major contributor to the development of cardiovascular disease (CVD) in diabetic patients (*1–3*). Several clinical trials have strongly supported the beneficial effect of rigorous control of blood pressure (BP) in type 2 diabetes mellitus (DM) patients (*4*, *5*). Based upon these observations, many guidelines have set lower target BP levels in hypertensive patients with type 2 DM (*6–8*).

Although the clinical importance of brachial BP is well established, it has been suggested that central pressure correlates more closely with cardiovascular risk than brachial pressure, and that they independently predict future cardiovascular events (*9*). Augmentation index (AI), the ratio of augmented pressure by the reflection pressure wave (ΔP) to the pulse pressure (PP), is significantly associated with the central BP (*10–13*).

Hypertensive patients have higher AI, hence their aortic BP is also elevated (*14*). Although diabetes is a major risk for atherosclerosis, there is controversy regarding the relationship between diabetes and AI. In a report of the Hoorn study, type 2 DM was associated with increased AI (*15*). On the other hand, it has also been reported that AI was not increased in DM patients, even if PP and pulse wave velocity (PWV)

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were increased (*16*).

Antihypertensive treatment significantly decreases AI in hypertensive patients, although there is a class-specific effect on AI (*9*). Angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs) are all reported to effectively reduce AI and central BP (*9*). In diabetic subjects, blood sugar (BS) control by insulin has been shown to significantly decrease AI (*17*), indicating BS is an important determinant of AI in diabetic patients. However, it remains to be determined which factor, BS or BP, is more important for AI and central BP in DM hypertensive patients. Furthermore, whether antihypertensive drugs have any class-specific effect on AI in DM hypertensive patients has never been studied.

Although the definition is different, AI can be obtained from the radial arterial wave form (*18*, *19*). It has been repeatedly shown that radial AI is closely associated with aortic AI (*14*, *18*). It has also been shown that radial SBP2 is very close to aortic SBP (*20*, *21*).

In the present study, we investigated the determinants of radial AI and SBP2, as an index of central BP, in DM patients with and without hypertension, with special emphasis on the effect of BS and BP. We also compared the effect of two classes of antihypertensive drugs, ACEIs or ARBs, CCBs, and their combination on AI and radial SBP2 in hypertensive DM patients.

Table 1. Clinical Characteristics of Study Subjects

	Total diabetic patients	Hypertensive diabetic patients
Number	194	123
Male/female	92/102	56/67
Age (years)	67.0±9.2	68.7±7.4
Height (cm)	154.7±9.8	153.9±9.8
Weight (kg)	58.0±12.6	59.9±13.2
BMI (kg/m^2)	24.1±3.9	25.1±3.8
AI (%)	88.9±12.3	89.1±11.9
SBP (mmHg)	141.1±18.7	145.8±17.7
DBP (mmHg)	75.4±10.9	76.6±10.5
MBP (mmHg)	97.3±11.6	99.7±10.7
SBP1 (mmHg)	139.4±18.4	143.9±17.2
SBP2 (mmHg)	132.5±19.3	136.7±18.3
Heart rate (beats/min)	73.4±11.4	73.8±11.5
Glucose (mg/dL)	157.9±63.1	159.1±63.2
HbA1c (%)	6.5±1.3	6.4±1.3
Total cholesterol (mg/dL)	202.7±35.8	204.5±34.0
HDL-cholesterol (mg/dL)	58.3±16.5	57.0±16.6
Triglycerides (mg/dL)	126.1±79.5	134.7±89.7
Smoking (current/former/never)	37/28/129	28/17/78

Values are mean±SD. BMI, body mass index; AI, augmentation index; SBP, systolic blood pressure; MBP, mean blood pressure; DBP, diastolic blood pressure; SBP1, first peak of SBP; SBP2, second peak of SBP; HDL, high-density lipoprotein.

Methods

Subjects

Participants were enrolled from among outpatients with type 2 DM in the medical department of Seiyo Municipal Nomura Hospital between June 2005 and April 2006. One hundred and ninety-four patients (92 men and 102 women, mean age 67±9 years) were enrolled in the study. Informed consent for the procedure was obtained from each patient. All procedures were approved by the Ethics Committee of Seiyo Municipal Nomura Hospital.

Arterial Waveform Analysis

AI was measured once in the left radial artery using an automated tonometric method (HEM-9000AI; Omron Healthcare, Kyoto, Japan), in an outpatient clinic with subjects in a sitting position after at least 5 min of rest. Brachial BP was measured once simultaneously in the right brachium with an oscillometric device incorporated into the HEM-9000AI. The HEM-9000AI device is programmed to automatically determine the pressure against the radial artery to obtain the optimal arterial waveform. AI was calculated as follows: (SBP2 − diastolic BP [DBP])/(first peak SBP − DBP) × 100 (%) (*18*, *19*). SBP2 was also calculated by calibration with brachial SBP. Mean BP (MBP) was obtained by the formula: MBP = (SBP + DBP × 2)/3. The reproducibility of the measurements was evaluated separately in 28 subjects. The within-subject coefficients of variation were 3.8±3.3% and 2.9±2.4% for radial AI and SBP2, respectively.

Biochemical Determination

On the day of AI measurements, blood was withdrawn for the determination of BS, HbA1c, total cholesterol, high-density lipoprotein (HDL) cholesterol and triglyceride. All patients were not fasting at the blood withdrawal. As an index of BS control status, HbA1c was used in the present study.

Statistical Analysis

All values are expressed as the means±SD, unless otherwise specified. Statistical analysis was performed using SPSS 10.0J (Statistical Package for Social Science, Inc., Chicago, USA). Pearson's correlation coefficients were used to analyze the association of clinical parameters. Stepwise regression analysis was employed to evaluate the independent parameters relating to AI. The relationships between antihypertensive drugs and radial AI and SBP2 were examined by a general linear model. Since AI and SBP2 are both indices obtained from SBP or PP, MBP was used in the analysis as an index for the BP parameters.

Table 2. Parameters Related to Radial AI in Total Population and Hypertensive Diabetic Patients (Pearson's Correlation Coefficient)

Variables	Total diabetic patients		Hypertensive diabetic patients	
	r	*p* value	*r*	*p* value
Age (years)	0.243	<0.001	0.196	0.030
Sex (female=1)	0.222	0.002	0.329	<0.001
Height (cm)	−0.332	<0.001	−0.385	<0.001
Weight (kg)	−0.294	<0.001	−0.242	0.007
BMI (kg/m^2)	−0.141	0.049	−0.041	0.653
Waist (cm)	−0.183	0.011	−0.147	0.105
Mean blood pressure (mmHg)	0.062	0.390	0.019	0.494
Heart rate (beats/min)	−0.478	<0.001	−0.437	<0.001
Glucose (mg/dL)	−0.183	0.011	−0.213	0.018
HbA1c (%)	−0.228	0.001	−0.213	0.018
Total cholesterol	0.028	0.694	0.154	0.089
HDL cholesterol	0.092	0.200	0.034	0.709
Triglyceride	0.053	0.466	0.094	0.302
Current smoking	−0.139	0.054	−0.249	<0.001
Use of antihypertensive drugs	0.031	0.663	—	—

AI, augmentation index; HDL, high-density lipoprotein.

A value of $p<0.05$ was defined as statistically significant.

Results

The clinical characteristics of the participants are summarized in Table 1. Of the 194 patients, 123 hypertensive diabetic patients were treated with antihypertensive drugs.

Parameters Associated with Radial AI in Type 2 Diabetic Patients

In a simple correlation analysis, radial AI showed a positive association with age, and a negative association with body height, body weight, body mass index, waist circumference, heart rate (HR), BS and HbA1c (Table 2). Women had significantly higher AI than men. Radial AI was not significantly associated with MBP in a simple correlation. However, stepwise regression analysis revealed that body height, MBP and HR were independent determinants of radial AI (Table 3). Similar findings were also observed in hypertensive diabetic patients (Tables 2, 3).

Parameters Associated with Radial SBP2 in Type 2 Diabetic Patients

SBP2 showed a positive association with age, body mass index (BMI), waist circumference, MBP and use of antihypertensive drugs and a negative association with body height (Table 4). Similar findings were also observed in hypertensive diabetic patients (Table 4).

Effect of Class of Antihypertensive Drugs on Radial AI in Hypertensive Diabetic Patients

We further investigated whether the effect of antihypertensive medication is class-dependent. We compared CCB and ACEI or ARB (ACEI/ARB) and their combination (CCB+ACEI/ARB). One hundred and twenty-three hypertensive diabetic patients treated with antihypertensive drugs were divided into three groups based on their prescribed drugs: ACEI/ARB ($n=37$), CCB ($n=31$), and CCB+ACEI/ARB ($n=55$). The distributions of β-blockers and diuretics were not different among the three groups. There was no difference in brachial SBP, DBP, HR, radial AI and SBP2 among the three groups (Table 5).

Discussion

AI is an index of the reflected pressure wave and is closely related to atherosclerosis, left ventricular afterload, diastolic coronary flow, central aortic BP, and hence future CVD and death (*9*, *22*). Risk factors for atherosclerosis, including hypertension, hyperlipidemia, smoking, and excessive alcohol consumption have all been shown to be associated with higher AI. Lifestyle modifications such as aerobic exercise (*23*, *24*), sodium restriction (*25*), and smoking cessation (*26*) have also been shown to decrease AI. However, studies of the association between type 2 DM and AI are inconclusive. It has been shown that DM is associated with higher AI (*15*), and BS control by insulin in DM patients significantly reduced AI (*17*). Acute BS elevation has also been shown to increase AI in part through oxidative stress (*27*). On the other hand, it has also been reported that AI was not higher (*28*) or

Table 3. Stepwise Regression Analysis of Radial AI in Total Population and Hypertensive Diabetic Patients

Variables	Total diabetic patients		Hypertensive diabetic patients	
	β	p value	β	p value
Age (years)				
Sex (female=1)				
Height (cm)	−0.217	<0.001	−0.360	<0.001
Weight (kg)				
Mean blood pressure (mmHg)	0.260	<0.001	0.243	0.004
Heart rate (beats/min)	−0.550	<0.001	−0.550	<0.001
HbA1c (%)				
Total cholesterol				
Current smoking				
Use of antihypertensive drugs			not included	
Overall r^2		0.421		0.449

Listed parameters were entered in the analysis. β and p values of statistically significant parameters are shown. AI, augmentation index.

Table 4. Parameters Related to SBP2 in Total Population and Hypertensive Diabetic Patients

Variables	Total diabetic patients		Hypertensive diabetic patients	
	r	p value	r	p value
Age (years)	0.274	<0.001	0.178	0.048
Sex (female=1)	0.119	0.098	0.210	0.020
Height (cm)	−0.166	0.021	−0.174	0.054
Weight (kg)	0.046	0.521	−0.017	0.848
Body mass index (kg/m^2)	0.187	0.009	0.113	0.211
Waist (cm)	0.148	0.039	0.046	0.613
Mean blood pressure (mmHg)	0.804	<0.001	0.768	<0.001
Heart rate (beats/min)	−0.062	0.388	−0.069	0.447
Glucose (mg/dL)	−0.084	0.242	−0.089	0.330
HbA1c (%)	−0.009	0.901	0.047	0.606
AI (%)	0.441	<0.001	0.489	<0.001
Total cholesterol	0.086	0.236	0.034	0.712
HDL cholesterol	−0.002	0.977	0.032	0.725
Triglyceride	0.093	0.195	0.030	0.745
Current smoking	0.017	0.811	−0.072	0.429
Use of antihypertensive drugs	0.294	<0.001	—	—

SBP2, second peak of systolic blood pressure; AI, augmentation index; HDL, high-density lipoprotein.

was even lower (*29*) in type 2 DM patients. Maple-Brown *et al*. (*29*) concluded that central obesity may explain the dissociation between AI and DM.

In the present study, body height negatively correlated with both AI and SBP2, while BMI and waist circumference showed negative correlations with AI and positive associations with SBP2. This dissociation may relate to the different degree of the association between AI and SBP with these anthropometric parameters. Although body height showed a significant negative association with AI, it was not correlated with SBP (r=−0.09, p=0.20). As a result, body height negatively correlated with SBP2 through an effect of AI. On the other hand, both BMI and waist circumference showed modest associations with AI (r=−0.14, p=0.0496, and r=−0.18, p=0.011, respectively), and stronger positive associations with SBP (r=0.23, p=0.0012, and r=0.21, p=0.033, respectively). Since SBP is a greater determinant of SBP2 compared with AI (β=0.90 and β=0.90, respectively), it is conceivable that BMI and waist circumference showed a positive association with SBP2 through an effect of SBP.

AI was negatively associated with BS, HbA1c and parameters of obesity, including body weight and waist circumference, in type 2 DM patients. However, after correction for other confounding parameters, neither glucose control nor indices of obesity were associated with AI. Radial AI was only associated with body height, HR, and MBP in multiple regression analysis. Well-known confounding factors including smoking status, age, and sex were not included in the

Table 5. Effect of Class of Antihypertensive Drugs on Hemodynamic Variables in Diabetic Patients with Treated Hypertension

	ACEI/ARB	CCB	ACEI/ARB+CCB	*p*
n	37	31	55	
SBP (mmHg)	144±23	142±16	149±14	0.11
DBP (mmHg)	75±10	77±10	77±11	0.72
SBP2 (mmHg)	134±22	135±17	140±16	0.28
Heart rate (beats/min)	72±8	74±15	75±11	0.64
AI (%)	87±11	92±11	89±13	0.24

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; SBP, systolic blood pressure; DBP, diastolic blood pressure; SBP2, second peak of SBP; AI, augmentation index.

equation. The specific characteristics of the study participants, including relatively advanced age (90% were >60 years), higher prevalence of antihypertensive medication in current smokers (75.5% *vs*. 60.5%, $p=0.012$), and higher HR in females than males (75.1±12.1 *vs*. 71.5±10.3 beats/min, $p=0.027$), may have concealed confounding influences of these factors. In fact, after matching HR between males and females, sex was an independent determinant of AI in addition to body height, MBP, and HR (Table A1 in Appendix). Furthermore, the possibility that the association with these confounding factors may be weak in DM patients still remains.

A benefit of tight BP control in hypertensive DM patients has been demonstrated in several clinical studies. The Hypertension Optimal Treatment (HOT) study, which included a subgroup of 1,501 DM patients, showed that the group assigned to the lowest diastolic BP target of 80 mmHg had a significantly reduced risk of cardiovascular death and major CVD compared with those whose target diastolic BP was 90 mmHg (*5*). In UK Prospective Diabetes Study (UKPDS) studies, it has been shown that tight BP control was more effective in reducing CVD events and death than tight BS control (*4*). The findings in the present study that radial AI was associated with SBP but not BS control status are consistent with the results of these studies.

Radial SBP2 was analyzed as a substitute for central aortic SBP, since radial SBP2 has been shown to be close to directly measured aortic SBP (*20*, *21*). It is conceivable that the pressure load on target organs, including the brain, heart, aorta, and kidney, would be more directly related to aortic BP than brachial BP (*9*). Supporting this hypothesis, aortic BP has been shown to be independently associated with composite endpoints in the Conduit Artery Function Evaluation (CAFE) study (*30*). In the CAFE study, amlodipine-based treatment showed a lower aortic BP level than atenolol-based treatment, even though there was no difference in brachial BP levels between the two treatment arms. Inhibition of the renin-angiotensin system, either by an ARB or ACEI, has been shown to have a favorable effect on AI and central BP (*22*, *31*). It has been postulated that the marked effects on aortic BP, which cannot be estimated from brachial BP, may partly explain why several classes of drugs appear to have effects beyond mere BP reduction.

In small scale clinical studies, CCB and ACEI/ARB showed no difference in the effect on AI and aortic BP in hypertensive patients (*32*). However, there have been no studies in hypertensive DM patients. In the present study, two classes of antihypertensive drugs, ACEI/ARB and CCB, had a similar effect on radial AI as well as radial SBP2. Furthermore, there was no additive effect of the two regimes on radial AI and radial SBP2. Unfortunately, we did not compare other classes of drugs in the present study, since only a small number of patients were taking diuretics and/or β-blockers. However, our findings may support the Japanese guidelines' recommendation of an ACEI or ARB and CCB as first line drugs for hypertensive DM patients (*6*).

There are several limitations in the present study. We measured AI and BP after 5 min of rest in a sitting position, which is in accordance with JSH 2004 guidelines (*6*). However, the possibility that a 5-min rest was not long enough to obtain steady state hemodynamic parameters still remains. Although the good reproducibility of the measurements was confirmed, the use of only a single determination of hemodynamic variables could also have caused fluctuations in the data. These points may have influenced the results. Furthermore, since the study had a cross-sectional, observational design, we cannot conclude that there was a causal relationship between BP and AI in DM patients. Although stepwise regression analysis showed that BP control rather than BS control was a significant determinant of AI in diabetic hypertensive patients, the overall r^2 values of the model were modest. These findings may indicate the inappropriateness of the models evaluated as well as the high noise ratio of the data in this study. A large scale controlled prospective study will be necessary to reconfirm our findings.

In summary, in patients with type 2 DM, radial AI was more directly related to BP level than DM control. In hypertensive DM patients, there was no difference between the effects of the two classes of antihypertensive drugs, ACEIs/ARBs and CCBs, on radial AI and SBP2. These findings indicate that tight BP control would be effective in reducing the augmentation and aortic BP, which could independently relate to CVD in DM patients.

Table A1. Stepwise Regression Analysis Performed for AI Corrected with Heart Rate Difference between Male and Female

Variables	Total diabetic patients		Hypertensive diabetic patients	
	β	p value	β	p value
Age (years)				
Sex (female=1)	0.344	<0.001	0.523	<0.001
Height (cm)	−0.181	0.008		
Weight (kg)				
Mean blood pressure (mmHg)	0.125	0.013	0.132	0.029
Heart rate (beats/min)	−0.674	<0.001	−0.690	<0.001
HbA1c (%)				
Total cholesterol				
Current smoking				
Use of antihypertensive drugs			not included	
Overall r^2		0.565		0.610

AI, augmentation index.

Appendix

AI was corrected with heart rate difference between male and female. Heart rate corrected AI was obtained from the linear regression line between AI and heart rate. After correction of heart rate difference between sexes, female was an independently associated with higher AI (Table A1).

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