Original Article

Postchallenge Plasma Glucose and Glycemic Spikes Are Associated with Pulse Pressure in Patients with Impaired Glucose Tolerance and Essential Hypertension

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Elevated pulse pressure (PP) is associated with an increased risk of cardiovascular events. We examined whether PP is associated with post-challenge hyperglycemia in Japanese patients with essential hypertension and impaired glucose tolerance (IGT). In a total of 70 untreated essential hypertensive patients (age: 57±4 years, mean±SD; males=35, females=35), 24-h ambulatory blood pressure (ABP) monitoring, 75 g oral glucose tolerance testing (OGTT), metabolic analysis and echocardiography were performed. Patients were categorized into a high PP group (PP≥60 mmHg, *n*=33) or a normal PP group (PP<60 mmHg, *n*=37). In all patients, 24-h systolic ABP, daytime systolic ABP, nighttime systolic ABP, and nighttime heart rate were significantly higher in the high PP group. Additionally, fasting immunoreactive insulin (F-IRI), homeostasis model assessment (HOMA) index, left ventricular mass index (LVMI) were also elevated in the high PP group. Finally, the high PP group exhibited impaired insulin secretion, increased post-challenge glucose concentrations and greater glucose spikes (PGS) during 75 g OGTT. Of the parameters measured, 24-h PP correlated positively with age, triglyceride, uric acid, F-IRI, HOMA index, 1-h postload glucose and insulin, 2-h postload glucose and insulin, PGS_{60}, PGS_{120}, PGS_{max}, LVMI, and deceleration time but correlated negatively with HDL-cholesterol and *E/A* ratio. Multiple regression analysis revealed that PP level was independently predicted by age, LVMI, and PGS_{120}. Our results show that age, LVMI, and PGS_{120} are significantly associated with high PP in Japanese patients with IGT and essential hypertension. (*Hypertens Res* 2008; 31: 1565–1571)

***Key Words*: pulse pressure, left ventricular mass index, post-challenge glucose spikes, impaired glucose tolerance, essential hypertension**

Introduction

Increasing evidence suggests that high pulse pressure (PP) indicates the presence of large arterial stiffness and is an independent predictor of cardiovascular disease in many populations. The prognostic utility of PP has been extended from elderly subjects with essential hypertension (*1*, *2*) to an unselected general population, including relatively young (*3*, *4*) and normotensive subjects (*5*). Furthermore, the Atherosclerosis Risk in Communities study (*6*) and the Hoorn study (*7*) demonstrated that arterial stiffness is increased in type 2 diabetic subjects compared with individuals with normal glucose tolerance, and this was confirmed using 24-h ambulatory

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blood pressure (ABP) monitoring of PP by van Dijk *et al*. (*8*).

Similarly insulin resistance, hyperglycemia (HG) and postprandial HG could be directly responsible for the excessive cardiovascular risk seen in patients with type 2 diabetes mellitus (*9*, *10*). Post-challenge HG, assessed by oral glucose tolerance test (OGTT), is an appropriate model of postprandial HG, and it is associated with an increased risk of cardiovascular disease (*11*). Post-challenge HG is more strongly associated with all-cause and cardiovascular mortality than fasting plasma glucose (FPG) in Caucasians (*12*) and Japanese subjects (*13*). In addition, post-challenge glucose spike (PGS) is the difference between post-challenge/prandial glucose concentration and FPG (*14*). PGS is more closely associated with atherosclerosis than either FPG or hemoglobin A1c (HbA1c) (*14*).

Impaired glucose tolerance (IGT) is a strong predictor of not only type 2 diabetes (*15*), but also cardiovascular disease and other diabetes complications (*12*, *13*).

Furthermore, in case of metabolic syndrome and pre-diabetes, IGT and hypertension were commonly observed. However, no studies have examined a relationship between PP and post-challenge HG and insulin resistance in patients with essential hypertension and IGT.

We hypothesized that increased PP would correlate with PGS in untreated essential hypertensive and IGT patients. In the present study, we analyzed the 24-h ABP, 75 g OGTT, metabolic profiles and echocardiographic findings in untreated essential hypertensive and IGT patients with high PP and normal PP. We also evaluated the predictors of 24-h PP in these patients.

Methods

Subjects

The blood pressure (BP) monitoring program recruited 245 consecutive subjects (135 men and 110 women, aged between 45 and 65 years) who were admitted to our department between January 2005 and December 2006. Of these 245 patients, 70 patients (age: 57±4 years, mean±SD; 35 men and 35 women) with untreated essential hypertension and IGT were enrolled in the current study. The clinical characteristics of the patients are summarized in Table 1. All subjects underwent routine laboratory tests including serum electrolytes, serum creatinine, blood urea nitrogen, FPG, fasting immunoreactive insulin (F-IRI), chest X-rays, ECG, and echocardiography.

Essential hypertension was defined as a mean 24-h systolic ABP (sABP) greater than 135 mmHg or a mean 24-h diastolic ABP (dABP) greater than 85 mmHg (*16*). Any patients with secondary hypertension, valvular heart disease, atrial fibrillation, congestive heart failure, renal failure, pulmonary disease, liver dysfunction, or a history of symptomatic cerebrovascular disease were excluded. None of the patients had been treated with antihypertensive agents, lipid-lowering medications, or anti-diabetic drugs prior to their participation in this study.

All subjects gave their written informed consent to participate in the study, and the study protocol was approved by the ethics committee of the Oita Red Cross Hospital.

Seventy-Five-Gram OGTT

Blood samples were obtained in the morning after an overnight (≥12 h) fast. The diagnosis of IGT was based on the results of the 75 g OGTT (*17*). Blood samples were taken 0, 30, 60, 90, and 120 min after load to determine the plasma glucose and insulin concentrations. Patients with FPG≥7.0 mmol/L, and/or 120-min postload glucose <7.8 mmol/L and ≥11.1mmol/L were excluded from the study. Therefore, all patients included in this study had IGT and untreated essential hypertension.

The following PGS parameters were calculated: PGS_{30} was the difference between 30-min postload glucose and FPG, PGS_{60} was the difference between 60-min postload glucose and FPG, PGS_{90} was the difference between 90-min postload glucose and FPG, PGS_{120} was the difference between 120-min postload glucose and FPG, and PGS_{max} was the difference between maximal plasma glucose and FPG.

Twenty-Four-Hour ABP Monitoring

During the screening process, the 24-h ABP was measured using the cuff-oscillometric method using an ABP monitoring system (TM-2425, A&D Co. Inc., Tokyo, Japan) with CO_2 gas–powered cuff inflation. The accuracy of this device has previously been validated (*18*). BP was measured every 30 min from 6:00 AM to 10:00 PM, and every 60 min from 10:00 PM to 6:00 AM on the following day (*19*). The mean BP value was computed for the awake period (between 6:00 AM and 10:00 PM) and the sleep period (between 10:00 PM and 6:00 AM) (*19*). The waking time, time taken to fall asleep, and quality of sleep were assessed by interview with each patient. Any patients who complained of sleep disturbances during ABP monitoring were excluded from the analysis.

Echocardiography

M-mode 2-dimensional echocardiography and cardiac Doppler recordings were obtained using a phase-array echo-Doppler system. Echocardiograms were obtained in the standard manner using standard parasternal, short axis and apical views. Left ventricular (LV) mass was calculated as previously described (*20*). The LV mass was calculated as $1.04\ ([LVIDd + IVSTd + PWTd]^3 - LVIDd^3) - 14$ (g), where LVIDd, LV internal dimension at end-diastole; IVSTd, interventricular septal thickness at end-diastole; and PWTd, posterior wall thickness at end-diastole. The LV mass was divided by the body surface area to calculate the LV mass index (LVMI). Pulsed Doppler recordings were made from

Table 1. Clinical Characteristics

	Normal PP	High PP	*p* value
Age (years)	56±5	58±4	n.s.
Gender (men/women)	20/17	15/18	n.s.
Body mass index (kg/m^2)	25.0±1.7	25.5±1.9	n.s.
24-h PP (mmHg)	55±4	66±5	<0.0001
24-h mean systolic ABP (mmHg)	149±6	159±6	<0.0001
24-h mean diastolic ABP (mmHg)	94±6	93±4	n.s.
24-h mean heart rate (beats/min)	68±5	70±6	n.s.
24-h overall mean BP (mmHg)	113±5	115±4	n.s.
Daytime systolic ABP (mmHg)	154±8	163±6	<0.0001
Daytime diastolic ABP (mmHg)	97±6	96±5	n.s.
Daytime heart rate (beats/min)	71±4	73±6	n.s.
Nighttime systolic ABP (mmHg)	136±8	148±11	<0.0001
Nighttime diastolic ABP (mmHg)	87±7	87±6	n.s.
Nighttime heart rate (beats/min)	59±5	63±7	0.0272

Data are mean±SD. PP, pulse pressure; ABP, ambulatory blood pressure; n.s., not significant.

Table 2. Metabolic Parameters

	Normal PP	High PP	*p* value
Total cholesterol (mmol/L)	5.3±1.0	5.6±0.8	n.s.
Triglyceride (mmol/L)	1.7±0.6	2.1±0.6	0.0114
HDL-C (mmol/L)	1.2±0.3	1.0±0.3	0.0364
Uric acid (mmol/L)	0.37±0.07	0.43±0.08	0.0013
Creatinine (mmol/L)	67.2±16.0	68.0±18.1	n.s.
FPG (mmol/L)	5.1±0.6	5.4±0.8	n.s.
F-IRI (pmol/L)	40.3±1.4	58.7±16.2	<0.0001
HOMA index	1.5±0.5	2.2±0.7	<0.0001
30-min postload glucose (mmol/L)	8.2±0.8	8.5±0.8	n.s.
30-min postload insulin (pmol/L)	254±65	217±96	n.s.
60-min postload glucose (mmol/L)	10.2±1.0	11.3±1.3	<0.0001
60-min postload insulin (pmol/L)	427±125	308±137	0.0003
90-min postload glucose (mmol/L)	9.8±0.8	10.5±1.0	0.0027
90-min postload insulin (pmol/L)	304±126	378±120	0.0140
120-min postload glucose (mmol/L)	8.8±0.7	9.8±1.0	<0.0001
120-min postload insulin (pmol/L)	278±135	399±150	0.0007
0–30-min PGS (mmol/L)	3.1±0.8	3.2±0.8	n.s.
0–60-min PGS (mmol/L)	5.4±1.0	5.8±1.2	n.s.
0–90-min PGS (mmol/L)	4.7±0.9	5.1±1.0	n.s.
0–120-min PGS (mmol/L)	3.7±0.8	4.4±1.1	0.0004
Max PGS (mmol/L)	5.1±1.0	6.1±1.2	0.0223
Hemoglobin A1c (%)	5.6±0.3	5.7±0.4	n.s.

Data are mean±SD. PP, pulse pressure; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; F-IRI, fasting immunoreactive insulin; HOMA, homeostasis model assessment; PGS, post-challenge glucose spikes; n.s., not significant.

the standard apical 4-chamber view. The mitral inflow velocity was recorded with the sample volume at the mitral annulus level; the average of ≥3 cardiac cycles was taken. The following measurements were taken: the peak velocity of early ventricular filling (*E*), the peak velocity of late ventricular filling (*A*), the ratio of these peak velocities (*E*/*A*), and the deceleration time.

Definition of Normal Pulse Pressure and High Pulse Pressure

Patients were divided into two groups based on 24-h ABP

Table 3. Echocardiographic Findings

	Normal PP	High PP	*p* value
EF (%)	69±4	70±5	n.s.
LVIDd (mm)	45±3	48±3	0.0016
LVIDs (mm)	30±2	31±3	0.0044
IVSTd (mm)	9.9±0.9	10.9±1.5	0.0020
PWTd (mm)	10.0±1.0	11.2±1.8	0.0005
LVMI (g/m^2)	115±19	147±33	<0.0001
E/*A* ratio	0.93±0.19	0.82±0.17	0.0181
Deceleration time (ms)	242±32	270±53	0.0081

Data are mean±SD. EF, ejection fraction; LVIDd, left ventricular internal dimension at end-diastole; LVIDs, left ventricular internal dimension at end-systole; IVSTd, interventricular septal thickness at end-diastole; PWTd, posterior wall thickness at end-diastole; LVMI, left ventricular mass index; *E*/*A* ratio, the ratio of peak of velocities of early to late ventricular filling.

monitoring. PP (mmHg) was calculated as (24-h sABP) – (24-h dABP). Normal PP was defined as 24-h PP<60 mmHg and high PP was defined as 24-h PP≥60 mmHg. This cut-off value of 60 mmHg was previously validated (*21*).

Insulin Resistance

Insulin resistance was evaluated by the homeostasis model assessment (HOMA) index (*22*):

$$\text{HOMA index} = (\text{fasting plasma insulin } [\mu\text{U/mL}] \times \text{fasting plasma glucose } [\text{mmol/L}])/22.5.$$

Statistical Analysis

Data are presented as mean±SD. The differences between the two groups were analyzed by the unpaired Student's *t*-test, χ^2 test, or Fisher's exact probability test.

A value of $p<0.05$ was considered statistically significant. Simple (Spearman's rank) correlation coefficients between 24-h PP and several variables were calculated, and a stepwise multiple regression analysis was then used to evaluate any independent associations. In our multivariate analysis, an *F* value≥4.00 was considered significant.

Results

After screening and exclusion of patients as described above, 70 patients were enrolled in this study with 33 qualifying for placement in the high 24-h PP group. As shown in Table 1, the mean age of patients in the two groups was similar, and no significant differences were observed between the two groups with respect to gender and body mass index. The 24-h mean dABP, heart rate, overall mean BP, daytime dABP and daytime heart rate were similar between the two groups.

Table 4. Correlations of Pulse Pressure with Other Variables

Parameters	Pulse pressure	
	r	*p* value
Age	0.313	0.0084
Triglyceride	0.327	0.0058
HDL-C	−0.270	0.0239
Uric acid	0.261	0.0294
F-IRI	0.320	0.0068
HOMA index	0.241	0.0447
90-min postload glucose	0.249	0.0376
120-min postload glucose	0.416	0.0003
120-min postload insulin	0.255	0.0329
0–60-min PGS	0.329	0.0054
0–90-min PGS	0.304	0.0104
0–120-min PGS	0.474	<0.0001
Max PGS	0.324	0.0063
IVSTd	0.307	0.0099
PWTd	0.312	0.0085
LVMI	0.367	0.0018
E/*A* ratio	−0.258	0.0307
Deceleration time	0.243	0.0427

Data are mean±SD. See Tables 1–3 for abbreviations.

In contrast, the 24-h mean sABP ($p<0.0001$), daytime sABP ($p<0.0001$), nighttime sABP ($p<0.0001$) and nighttime heart rate ($p=0.0272$) were higher in the high 24-h PP group than in the normal 24-h PP group.

When metabolic parameters were compared between the two groups, total plasma cholesterol levels were not significantly different (Table 2). However, the triglyceride ($p=0.0114$) and uric acid ($p=0.0013$) levels were higher in the high 24-h PP group than in the normal 24-h PP group, but the plasma high-density lipoprotein (HDL)-cholesterol was lower in the high 24-h PP group than in the normal 24-h PP group ($p=0.0364$).

The F-IRI ($p<0.0001$), HOMA index ($p<0.0001$), 1-h postload glucose ($p<0.0001$), 1-h postload insulin ($p=0.0003$), 2-h postload glucose ($p<0.0001$), 2-h postload insulin ($p=0.0007$), and PGS_{60}, ($p=0.0054$), PGS_{120} ($p=0.0004$), and PGS_{max} ($p=0.0009$) were all higher in the high 24-h PP group than in the normal 24-h PP group. The FPG, HbA1c, and plasma creatinine were not significantly different between the two groups.

An analysis of echocardiographic findings demonstrated that the LV dimensions at end-diastole and end-systole ($p=0.0016$ and $p=0.0044$, respectively), interventricular septal thickness and posterior wall thickness at end-diastole ($p=0.0022$ and $p=0.0005$, respectively), and the LVMI ($p<0.0001$) were greater in the high 24-h PP group than in the normal 24-h PP group (Table 3). However, the two groups had similar LV ejection fractions. With respect to the LV diastolic function, the *E*/*A* ratio was lower ($p=0.0181$) and

Table 5. Stepwise Regression Analyses of Pulse Pressure and Other Variables

Independent variables	Regression coefficient	Standard error	Standard regression coefficient	*F* value
To pulse pressure intercept	13.785			
Age	0.436	0.162	0.262	7.245
LVMI	0.068	0.024	0.284	8.343
0–120-min PGS	0.171	0.041	0.408	17.145

LVMI, left ventricle mass index; PGS, post-challenge glucose spikes.

the deceleration time was greater ($p = 0.0081$) in the high 24-h PP group than in the normal 24-h PP group.

We next compared all of the measured parameters by univariate analysis (Table 4) for all patients in both groups. The results of this analysis showed that 24-h PP correlated positively with age, triglyceride, uric acid, F-IRI, HOMA index, 1-h postload glucose and insulin, 2-h postload glucose and insulin, PGS_{60}, PGS_{120}, PGS_{max}, IVSTd, PWTd, LVMI and deceleration time. They also revealed that 24-h PP correlated negatively with HDL-cholesterol and the *E*/*A* ratio. A multiple regression analysis was performed using the stepwise procedure. Based on this analysis, the level of 24-h PP was significantly associated with age, LVMI, and PGS_{120} (Table 5).

Discussion

The relationship between the metabolic changes associated with insulin resistance and hyperglycemia and elevated PP remains somewhat unclear in patients with hypertension and IGT. In the present study, we performed 24-h ABP monitoring and 75 g OGTT, and demonstrated a more significant correlation between 24-h PP and post-challenge HG and PGS than FBS, F-IRI and HOMA index. To our knowledge, this is the first report to show that PGS_{120} is significantly associated with 24-h PP in essential hypertensive Japanese patients with IGT.

Post-challenge HG, assessed by OGTT, is more strongly associated with all-cause and cardiovascular mortality than FPG in Caucasians (*12*) and Japanese subjects (*13*). In addition, PGS_{max} and plasma glucose are more closely linked to atherosclerosis than FPG and HbA1c level (*14*). However, it was unclear whether 24-h PP is associated with OGTT parameters such as post-challenge HG and PGS. We demonstrated that elevated 24-h PP was more closely associated with post-challenge HG and PGS than F-IRI and HOMA index in essential hypertensive patients with IGT. In Caucasian populations, decreased insulin sensitivity is the primary metabolic defect underlying glucose intolerance; however, impaired insulin secretion accounts for most glucose intolerance in Japanese patients (*23*, *24*). As a consequence, Caucasian diabetic patients are often also obese with increased FPG concentrations, whereas their Japanese counterparts are relatively lean and exhibit normal FPG levels but increased postprandial hyperglycemia. The characteristics of our study subjects were consistent with these general trends in the Japanese population with glucose intolerance (Tables 1, 2). These trends were more pronounced in the high 24-h PP group, which had a greater degree of post-challenge HG and PGS. The high PP group had a high HOMA index and a delayed hypersecretion of IRI, indicating that they might have insulin resistance although they are not obese. Thus, there may be a relationship between HG, PGS and/or impaired insulin secretion following OGTT in hypertensive Japanese patients with IGT and elevated PP.

The mechanism(s) underlying the relationship between 24-h PP and postprandial HG remain unclear. Post-challenge HG and high PGS can be considered surrogate markers of large plasma glucose oscillations after meals, and oscillatory HG may cause atherosclerosis and high PP *via* increased systemic cytokine secretion. Esposito *et al*. (*25*) showed that oscillatory HG affects cytokine levels to a greater extent than continuous HG, and this is more pronounced in patients with IGT. Additionally, increased levels of cytokines such as IL-6 and TNF-α are associated with increased cardiovascular disease (*26*). Postprandial HG is associated with increased oxidative stress (*27–29*) and endothelial dysfunction (*30*, *31*), and these are thought to promote the development of atherosclerosis (*31*) and hypertension (*31*, *32*). Furthermore, HG is related to decreased blood flow to skeletal muscle (*33*). Therefore, a high PP might result in endothelial dysfunction and, hence, a decreased blood flow to skeletal muscle, resulting in decreased glucose utilization.

Finally, sustained HG may affect cellular feedback loops, leading to physiological changes to counteract sustained, high glucose levels. However, intermittently elevated glucose concentrations may reduce such adaptations, leading to more pronounced toxicity (*34*).

In relatively young subjects with type 2 diabetes, sBP and dBP were consistently higher in the subgroup with a high PP (*35*). In middle-aged subjects with hypertension and IGT, however, we found that daytime and nighttime sBPs were significantly higher in the high PP group while dBPs were similar between the two groups. These differences are not easily explained by the age-related progression of large artery stiffness alone.

In subjects with IGT and essential hypertension, patients who had a high PP of more than 60 mmHg revealed higher 24-h sABP and daytime sABP. In addition, the subjects have a nighttime sABP associated with a higher nighttime heart rate in comparison to those with normal PP in the present

study. These features might reflect the hypertensive who has greater sympathetic nervous activity and/or is non-dipper hypertension. Tomiyama *et al*. (*36*) recently reported that heart rate elevation precedes the development of full-blown metabolic syndrome in subjects with premetabolic syndrome. In addition, we have previously shown that when examining non-dippers with increased insulin resistance, non-dippers have higher nighttime sABP and a nighttime heart rate than dippers (*37*, *38*). Furthermore, Facchini *et al*. (*39*) observed a significant correlation between elevated nocturnal heart rate and insulin resistance accompanied with hyperinsulinemia.

Several studies have shown that increased 24-h PP is associated with LV hypertrophy (LVH) (*40*, *41*). Khatter *et al*. (*40*) reported that LVMI was related to baseline 24-h PP using 24-h intraarterial BP monitoring. Jokiniitty *et al*. (*41*) found that during 10 years of follow up, 24-h PP was the best predictor of the future LV mass and the change in the LV mass. In the present study, we confirmed LVMI as an independent risk factor for high PP in Japanese hypertensive patients with IGT. Although the precise link between LVMI and PP remains unclear, there are several plausible pathophysiological explanations. Increased PP causes a disproportionate increase in end-systolic stress and, thereby, promotes the development of cardiac hypertrophy (*42*). Alternatively, there was an association between PP and acetylcholine (Ach)-stimulated forearm blood flow in a cohort of patients with untreated essential hypertension, suggesting that PP is an independent risk factor for endothelial dysfunction (*43*). Endothelial dysfunction increased aortic stiffness and correlated with LVH (*44*).

Taken together, the novel and important findings of the present study demonstrate that PP can be used as an early marker of atherosclerosis in patients with IGT.

There are several limitations to this study. First of all, the study included a relatively small number of patients. Further studies should examine a greater number of subjects. Second, previous studies examined the relationship of PP, microalbuminemia (*45*), and autonomic dysfunction (*46*). Cytokine levels, which may be affected by HG, were not evaluated in the present study. Therefore, further study is required to examine a possible relationship between PP, microalbuminemia, autonomic dysfunction and cytokine levels in hypertensive patients with IGT.

In conclusion, we show that age, LVMI, and PGS_{120} are significantly associated with high PP in Japanese patients with IGT and essential hypertension.

As such, therapeutic modulation of PGS and LVH might provide additional benefits to conventional antihypertensive treatment in hypertensive patients with IGT.

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