Original Article

Regional Arterial Stiffness Associated with Ischemic Heart Disease in Type 2 Diabetes Mellitus

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Arterial stiffness is increased in type 2 diabetes mellitus, and diabetes preferentially affects arterial stiffness of the central (elastic, capacitive) over peripheral (muscular, conduit) arteries. We hypothesized that arterial stiffness of the central artery may be more closely associated with ischemic heart disease (IHD) than stiffness of peripheral arteries in type 2 diabetes mellitus. The subjects were 595 type 2 diabetes patients including 70 with IHD. Arterial stiffness was measured as pulse wave velocity (PWV) in the heart-carotid, heart-femoral, heart-brachial, and femoral-ankle regions. The PWV values of the four segments correlated with each other in patients without IHD. However, the correlations were less impressive in those with IHD, suggesting unequal stiffening of regional arteries in IHD. As compared with patients without IHD, the IHD group showed significantly higher PWV values of the four arterial segments, particularly of the heart-femoral region. The presence of IHD was significantly associated with higher heart-femoral PWV, and this association remained significant and independent of other factors in a multiple logistic regression analysis. Pulse pressure was more strongly correlated with PWV of the heart-femoral than other arterial regions. Thus, diabetic patients with IHD have increased stiffness of arteries, particularly of the aorta, supporting the concept that central arterial stiffness plays an important role in the development of IHD.

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Key words; Arteriosclerosis, Pulse wave velocity (PWV), Coronary artery disease, Diabetes mellitus

Introduction

Diabetes mellitus is an independent risk factor of cardiovascular disease (CVD). The risk of CVD is several times higher in diabetic patients than non- diabetic subjects[1, 2]. The increased risk of CVD in diabetic patients is due, at least partly, to advanced atherosclerotic vascular changes. In addition to morphological thickening[3-5], patients with type 2 diabetes mellitus have increased stiffness of large arteries[5-7]. Arterial stiffness is an independent predictor for death from CVD as shown in high risk populations[8-10] including those with type 2 diabetes mellitus[11].

Arterial stiffness is a systemic change, but there are regional differences in arterial stiffening. Recently, we[12] found that type 2 diabetes mellitus preferentially affects arterial stiffness of the aorta and carotid arteries over the upper and lower limb arteries. In contrast, male gender was associated with increased stiffness of lower limb arteries[12], and hormone replacement therapy was shown to decrease stiffness of peripheral but not central arteries in postmenopausal women[13-15]. So far, little is known about the clinical importance of such regional differences in arterial stiffening. In patients with coronary artery disease, time to ST-segment depression during a treadmill exercise test was inversely correlated with aortic pulse wave velocity (PWV) but not with femoral-tibial PWV[16]. According to a very recent report by Pannier *et al.*[17], stiffness of the aorta, but not of the upper limb or lower limb arteries, was an independent predictor for death from

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Table 1. Characteristics of the subjects

	IHD (−)	IHD (+)	*P* value
Number of subjects	525	70	–
Gender (% male)	57	76	0.006*
Age (years)	61 ± 10.3	67 ± 7.7	< 0.0001
Smoking (% smoker)	51	67	0.012*
Duration of diabetes mellitus (years)	10.7 ± 8.6	16.3 ± 10.9	< 0.0001
Body mass index (kg/m^2)	24.0 ± 3.8	23.8 ± 3.2	0.673
Fasting plasma glucose (mmol/L)	8.1 ± 2.6	7.7 ± 2.4	0.259
Hemoglobin A1c (%)	8.0 ± 1.8	8.5 ± 1.7	0.054
HDL-cholesterol (mmol/L)	1.32 ± 0.39	1.19 ± 0.36	0.009
Non-HDL-cholesterol (mmol/L)	3.93 ± 1.22	3.57 ± 0.93	0.016
Serum creatinine (μmol/L)	97 ± 115	133 ± 133	0.048
Systolic BP (mmHg)	134 ± 20	134 ± 21	0.951
Diastolic BP (mmHg)	78 ± 11	74 ± 12	0.004
Pulse pressure (mmHg)	55 ± 14	59 ± 15	0.039
Ankle brachial pressure Index	1.15 ± 0.13	1.05 ± 0.20	< 0.0001
Use of antihypertensives (%)	46	86	< 0.0001
Use of lipid-lowering drugs (%)	35	50	0.016
Use of insulin injection (%)	24	50	< 0.0001

Mean ± SD.
P values are from an analysis of variance or *chi-squared test.
Abbreviations: HDL, high-density lipoprotein; BP, blood pressure.

CVD in a cohort of hemodialysis patients. Thus, it is probable that the effect of arterial stiffness on CVD differs among arterial regions.

So far, no study in the literature has examined the possible relationship between CVD and regional arterial stiffness in patients with type 2 diabetes mellitus. The aim of the present study is to examine whether ischemic heart disease is more closely associated with stiffness of central than peripheral arteries in type 2 diabetic patients.

Subjects and Methods

Subjects

The subjects were 595 consecutive patients with type 2 diabetes mellitus who underwent regional PWV measurements at the Diabetes Center, Osaka City University Hospital. Clinical characteristics of the subjects are given in **Table 1**. Informed consent was obtained from all study participants, and this study was approved by the Institutional Ethics Committee.

The Diagnosis of type 2 diabetes mellitus was made according to the criteria of the American Diabetes Association[18]. Duration of diabetes, treatments for diabetes, hypertension, and hyperlipidemia are given in **Table 1**.

Ischemic heart disease (IHD) was diagnosed by carefully taking a past history of myocardial infarction and/or angina pectoris, and by the presence of ischemic changes in the electrocardiogram or myocardial scintigraph at rest and/or during exercise. In some cases, the diagnosis was confirmed by coronary angiography. IHD was diagnosed in 70 out of the 595 patients.

PWV and Blood Pressure Measurements

PWV and blood pressure were measured in the supine position after 5 minutes bed rest using an automatic waveform analyzer (model BP-203RPE, Colin, Komaki, Japan) as previously described[12]. Pressure waveforms of the brachial and tibial arteries were recorded by an oscillometric method using occlusion/sensing cuffs adapted to both the arms and both the ankles. Pressure waveforms of the carotid and femoral arteries were recorded using multi-element tonometry sensors placed at the left carotid and the left femoral arteries. The Electrocardiogram was monitored with electrodes placed on both wrists. Heart sounds S1 and S2 were detected by a microphone set on the left edge of the sternum at the third intercostal space. The waveform analyzer reports PWV of the heart-femoral (hf PWV), heart-carotid (hc PWV), heart-brachial (hb PWV), and femoral-ankle (fa PWV) arterial segments by simultaneously measuring time intervals for pulse waves to travel along the corresponding arterial paths. The path lengths were estimated based on the height. The interobservation variations (coefficients of variation) were 6.0%, 3.3%, 4.9%, and 3.3% for hc PWV, hb PWV, hf PWV, and fa PWV, respectively.

Biochemical Measurements

Blood was drawn in the morning after an overnight fast of at least 12 hours. Hemoglobin A_{1c} (HbA_{1c}) levels were measured by high performance liquid chromatography, and plasma glucose levels, by a glucose oxidase method. Other measurements were done by routine laboratory methods. The Non-high-density lipoprotein (non-HDL) cholesterol level was calculated by subtracting the HDL cholesterol level from the total level of cholesterol.

Statistics

Data were summarized as a percentage or as the mean ± standard deviation (SD) as appropriate. The Difference in prevalence was evaluated with the chi-square test. The Difference between mean values was assessed by analysis of variance (ANOVA). The Correlation between two continuous variables was examined by linear regression analysis. Multiple regression analysis was used to assess independent associations between one dependent and two or more independent variables. Multiple logistic regression analysis was employed to determine factors that were independently associated with categories of a dependent variable. Dummy variables were used for gender (female = 0, male = 1), presence of IHD (no = 0, yes = 1), smoking (non-smoker = 0, smoker = 1), use of antihypertensives (no = 0, yes = 1) and use of lipid-lowering drugs (no = 0, yes = 1). *P* values less than 0.05 were considered significant. All these analyses were performed using statistics software for Windows (StatView 5, SAS Institute Inc., Cary, NC, USA) on personal computers.

Results

Clinical Characteristics of the Two Groups

We compared clinical characteristics between the two groups with and without IHD (**Table 1**). A Significant difference was found in the prevalence of gender, smokers, the use of medications for hypertension and hyperlipidemia, and the use of insulin injection for diabetes mellitus. Also, the IHD group showed a higher age, a longer duration of diabetes, a higher level of serum creatinine, and a higher pulse pressure. In contrast, the patients with IHD showed lower levels of HDL cholesterol, non-HDL cholesterol, diastolic BP and ABI. There was no significant difference in body mass index (BMI), HbA_{1c}, or systolic BP.

Correlation between Regional PWV Values

In the patients without IHD, PWV values of the four arterial regions showed a significant positive correlation as shown in **Fig. 1**. In the patients with IHD, however, the correlations were less impressive, and the correlation was not statistically significant between hf PWV and fa PWV.

Changes in Regional PWV Associated with IHD

Fig. 2 shows a comparison of each regional PWV between the patients with and without IHD. The IHD group had significantly higher hf PWV and hb PWV, whereas they had a significantly lower fa PWV as compared with those without IHD. No significant difference was noticed in hc PWV between the two groups.

Independent Association between IHD and Regional PWV

Because the two groups differed in the clinical characteristics that may affect PWV, multiple regression models were applied in order to correct for the possible confounders (**Table 2**). The association between IHD and hf PWV remained significant even after adjustments for age, gender, smoking, diabetic duration, systolic BP, HbA_{1c}, HDL cholesterol, non-HDL cholesterol, serum creatinine, and use of antihypertensive and lipid-lowering medications. Although the association between IHD and hb PWV was not significant in the multivariate model, the inverse association with IHD and fa PWV remained significant. Since hemodynamically significant stenosis of leg arteries reduces PWV[19], the patients with reduced ABI (<0.90) were excluded from further analysis. Then, the association between IHD and fa PWV was no longer significant, whereas the positive association between IHD and hf PWV was again significant.

Multiple Logistic Regression Analysis

The association between IHD and hf PWV was further evaluated using multiple logistic regression models, where the dependent variable was the presence or absence of IHD, and the explanatory (independent) variables were age, male gender, smoking, diabetic duration, systolic blood pressure, HbA_{1c}, HDL-cholesterol, non-HDL cholesterol, serum creatinine, and use of antihypertensive and lipid-lowering medications, in addition to each regional PWV. As shown in **Table 3**, hf PWV showed a highly significant association with the presence of IHD independent of the other con-

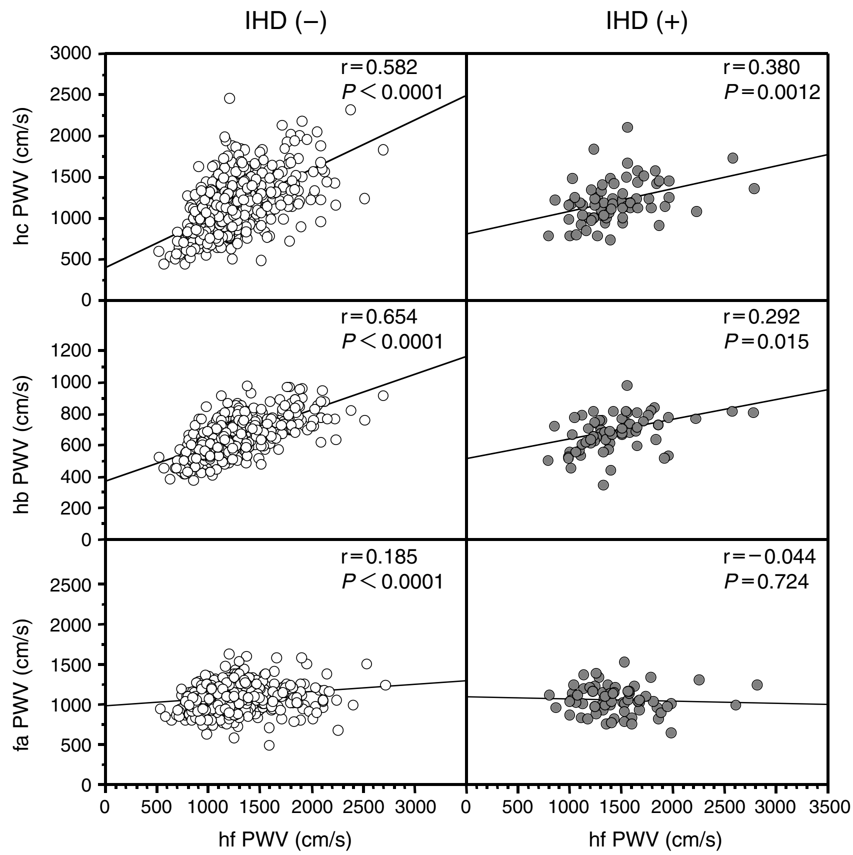

Fig. 1. Comparison of regional PWV between type 2 diabetes patients with and without ischemic heart disease.

P and r values are from a simple linear regression analysis.
Abbreviations: IHD, ischemic heart disease; PWV, pulse wave velocity; hc, heart-carotid; hf, heart-femoral; hb, heart-brachial; fa, femoral-ankle.

founding variables, indicating that the 100 cm/s increase in hf PWV increased the risk of IHD by 14.5% (95% confidence interval, 3.2-27.0%). In contrast, the risk of IHD did not increase significantly with the change in hc PWV, hb PWV or fa PWV in these models.

Correlation of Pulse Pressure with Regional Arterial Stiffness

We examined the possible difference in the correlation of pulse pressure with regional PWV (**Table 4**). In the subjects overall, pulse pressure showed the highest coefficient of correlation with hf PWV. This was also true for the subgroups with and without IHD. The Correlations between pulse pressure and PWV of other arterial segments were less impressive and hc PWV and fa PWV did not significantly correlate with pulse pressure in the IHD group.

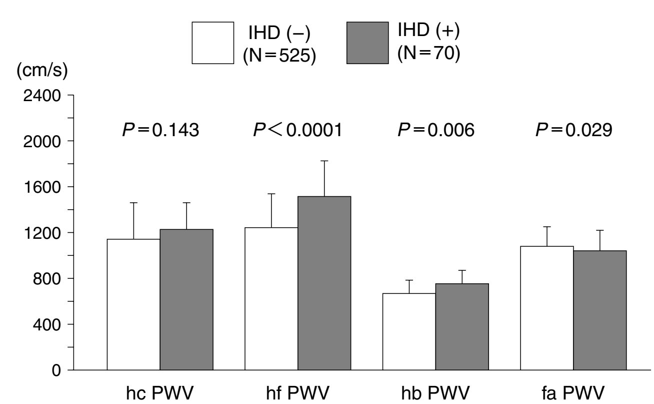

Fig. 2. Comparison of regional PWV between type 2 diabetes patients with and without ischemic heart disease.

Mean ± SD.
P values are from an analysis of variance.
Abbreviations: IHD, ischemic heart disease; PWV, pulse wave velocity; hc, heart-carotid; hf, heart-femoral; hb, heart-brachial; fa, femoral-ankle.

Table 2. Multiple regression analysis of factors related to regional PWV in the total subjects overall

	hc PWV	hf PWV	hb PWV	fa PWV
Age	0.311***	0.344***	0.295***	0.157***
Male gender	0.130*	0.133***	0.174***	0.080
Smoking	0.021	−0.020	−0.012	−0.075
Duration of diabetes mellitus	−0.056	0.098**	−0.002	−0.125**
Systolic blood pressure	0.238***	0.525***	0.532***	0.139*
Diastolic blood pressure	0.098	−0.045	0.002	0.325***
Hemoglobin A1c	0.059	0.099**	0.007	0.115**
HDL-cholesterol	0.045	0.002	−0.002	0.021
Non-HDL-cholesterol	0.049	0.046	0.031	−0.060
Serum creatinine	0.024	0.093**	−0.031	−0.066
Use of antihypertensives	0.077	0.016	−0.036	0.033
Use of lipid-lowering drugs	0.046	0.010	0.010	−0.044
IHD	−0.016	0.081*	0.053	−0.067
R^2	0.234***	0.517***	0.396***	0.212***

The table gives standard regression coefficients (β values) and level of significance.
Dummy variables were used for gender (female=0, male=1), presence of IHD (no=0, yes=1), smoking (non-smoker=0, smoker=1), use of antihypertensives (no=0, yes=1) and use of lipid-lowering drugs (no=0, yes=1).
Abbreviations: BP, blood pressure; HDL, high-density lipoprotein-cholesterol; R^2, coefficient of determination; IHD, ischemic heart disease.
***$P<0.001$, **$P<0.01$, *$P<0.05$.

Table 3. Multiple logistic regression analysis of independent factors associated with IHD

	Model 1	Model 2	Model 3	Model 4
Age (per 1 year)	1.036 (0.994-1.080)	1.051*(1.010-1.093)	1.045*(1.003-1.088)	1.051*(1.010-1.093)
Gender (male vs. female)	1.767 (0.785-3.975)	1.981 (0.880-4.459)	1.653 (0.734-3.723)	2.403* (1.052-5.487)
Smoking (smoker vs. non-smoker)	1.411 (0.695-2.864)	1.430 (0.709-2.888)	1.533 (0.753-3.119)	1.367 (0.667-2.798)
Duration of diabetes mellitus (per 1 year)	1.023 (0.991-1.056)	1.027 (0.996-1.060)	1.023 (0.990-1.056)	1.019 (0.987-1.052)
Systolic blood pressure (per 1 mmHg)	0.993 (0.967-1.019)	1.004 (0.979-1.029)	0.998 (0.973-1.025)	1.005 (0.980-1.031)
Diastolic blood pressure (per 1 mmHg)	0.970 (0.928-1.015)	0.970 (0.928-1.015)	0.970 (0.928-1.014)	0.983 (0.938-1.029)
Hemoglobin A1c (per 1%)	1.194*(1.010-1.413)	1.217*(1.032-1.435)	1.215*(1.030-1.434)	1.273**(1.074-1.510)
HDL-cholesterol (per 1 mmol/L)	0.980 (0.957-1.003)	0.980 (0.957-1.003)	0.978 (0.955-1.002)	0.979 (0.956-1.003)
Non-HDL-cholesterol (per 1 mmol/L)	0.994 (0.986-1.002)	0.995 (0.986-1.003)	0.994 (0.986-1.002)	0.994 (0.986-1.002)
Serum creatinine (per 1 μmol/L)	0.992 (0.814-1.209)	1.025 (0.844-1.243)	1.033 (0.849-1.258)	1.029 (0.849-1.247)
Use of antihypertensives (yes vs. no)	5.708***(2.627-12.40)	5.684***(2.601-12.42)	5.654***(2.581-12.39)	5.573***(2.545-12.20)
Use of lipid-lowering drugs (yes vs. no)	1.264 (0.695-2.297)	1.257 (0.696-2.272)	1.239 (0.683-2.248)	1.407 (0.767-2.578)
hf PWV (per 100 cm/s)	1.142*(1.031-1.265)	_	_	_
hc PWV (per 100 cm/s)	_	1.000 (0.911-1.098)	_	_
hb PWV (per 100 cm/s)	_	_	1.214 (0.931-1.582)	_
fa PWV (per 100 cm/s)	_	_	_	0.851 (0.700-1.034)
R^2	0.238***	0.222***	0.224***	0.228***

The table gives odds ratios (95% confidence intervals) for the presence of ischemic heart disease (IHD). Dummy variables were entered for gender (female=0, male=1), presence of IHD (no=0, yes=1), smoking (non-smoker=0, smoker=1), use of antihypertensives (no=0, yes=1) and use of lipid-lowering drugs (no=0, yes=1).
Abbreviations: BP, blood pressure; HDL, high-density lipoprotein; PWV, pulse wave velocity; hf, hear-femoral; hc, heart-carotid; hb, heart-brachial; fa, femoral-ankle; R^2, coefficient of determination.
***$P<0.001$, **$P<0.01$, *$P<0.05$.

Table 4. Correlation between pulse pressure and regional PWV

	Total subjects	IHD (−)	IHD (+)
hc PWV	0.296***	0.312***	0.119 (NS)
hf PWV	0.550***	0.542***	0.570***
hb PWV	0.478***	0.513***	0.275*
fa PWV	0.168***	0.183***	0.133 (NS)

The table gives simple correlation coefficients of pulse pressure and regional PWV. Note that pulse pressure was most strongly correlated with PWV of the heart-femoral (aortic) segment regardless of the presence of ischemic heart disease.
Abbreviations: IHD, ischemic heart disease; PWV, pulse wave velocity; hf, heart-femoral; hc, heart-carotid; hb, heart-brachial; fa, femoral-ankle.
*$p<0.05$, ***$p<0.001$ by simple linear regression analysis.

Discussion

In the present study, we measured regional PWV in four segments of arteries to examine whether IHD is more closely associated with stiffness of central than peripheral arteries in patients with type 2 diabetes mellitus. In patients without IHD, the regional PWV values correlated significantly in a positive manner. In the group having IHD, however, this correlation was less impressive, and the correlation between hf PWV and fa PWV was not significant, suggesting arterial stiffening did not occur equally among the arterial regions in patients with IHD. In fact, the increase in PWV in the IHD patients was most significant in the heart-femoral segment, and the positive association between IHD and PWV was significant only in the heart-femoral segment when an adjustment was made for other confounders. These results indicate the closest association of IHD with stiffness of the aorta among the four arterial regions.

There is only a limited amount of information available about the role of regional arterial stiffness in IHD and other vascular complications. A recent study by Kingwell *et al.*[16] revealed in patients with coronary artery disease that time to ST-segment depression during a treadmill exercise test was inversely correlated with PWV of the aorta but not with the femoral-tibial segment. In A more recent report by Pannier *et al.*[17], stiffness of the aorta, but not of the upper limb or lower limb arteries, was an independent predictor for death from CVD in a cohort of hemodialysis patients. These studies in mostly nondiabetic subjects are in good agreement with the present finding that IHD is more closely associated with aortic PWV than PWV of other arterial regions in patients with type 2 diabetes mellitus. Taken together, these studies indicate the importance of central arterial stiffness in cardiovascular disease regardless of the presence of diabetes mellitus.

There are at least two mechanisms that can explain the close association between IHD and stiffness of central arteries as reviewed previously[20]. First, stiffening of central or capacitive arteries increases systolic blood pressure, left ventricular afterload and hypertrophy, and myocardial oxygen consumption. These changes favor myocardial ischemia on the one hand. On the other hand, stiffening of central arteries decreases diastolic blood pressure and coronary perfusion which also induces myocardial ischemia. These hemodynamic changes in the systole and diastole can be reflected by increased pulse pressure. We examined the relationship between pulse pressure and regional arterial stiffness, and found the strongest correlation of pulse pressure with hf PWV or aortic stiffness. This is additional support for the more important role of arterial stiffness of central rather than peripheral arteries in coronary hemodynamics.

Although the present results emphasize the role of central arterial stiffness in IHD, stiffening of peripheral arteries does affect peripheral circulation. We previously showed that an increased stiffness index β of the femoral artery was associated with a reduction in transcutaneous oxygen tension of the feet during treadmill exercise[21] as well as ischemic symptoms of lower extremities[7]. In addition, Suzuki *et al.* reported that increased PWV of leg arteries was associated with a lowered blood flow of popliteal arteries determined by magnetic resonance[22]. Thus, these studies indicate different influences of regional arterial stiffness on clinical manifestations.

Previous studies indicated that the risk factors for stiffening of central and peripheral arteries are different. Age and diabetes mellitus are factors preferentially associated with central arterial stiffness, whereas male gender is associated with an increased PWV of lower limb arteries[12]. Treatment with a cross-link breaker of advanced glycation end-products (AGEs) was followed by a reduction of aortic PWV but not systemic arterial resistance[23]. In contrast, hormone replacement therapy for post-menopausal women selectively reduced stiffness of peripheral arteries[13-15]. Similarly, lipid-lowering with a statin reduced PWV of leg arteries without significantly changing PWV of the aorta[24]. Taken together, these studies have two implications. First, stiffness of central and peripheral arteries is governed by different factors. Clinical factors and medications that affect vascular wall matrix proteins and endothelial functions appear to have a link with central and peripheral arterial stiffness, respectively. Second, we should be careful about arterial regions when assessing arterial stiffness.

Although we measured hf PWV as an index for central arterial stiffness in the present study, other more simple measures may be used for screening purposes in routine clinical practice and epidemiological studies. One candidate is brachial-ankle PWV (ba PWV), an integrated index for stiffness of both central and peripheral arteries, that can be measured without sensors for carotid and femoral pulse waves. Kitahara *et al.*[25] have recently shown that a high ba PWV is predictive of mortality in hemodialysis patients. Another candidate is pulse pressure. Pulse pressure is known as an independent predictor of cardiovascular mortality[26], and it correlates more closely with PWV of the aorta than PWV of other arterial segments as shown in the present study.

There are a few limitations to this study. First, although the diagnosis of IHD was carefully based on a combination of past history, symptoms, blood chemistry, electrocardiography, scintigraphy, and coronary angiography, angiography was not performed for all cases. Second, this study is not longitudinal but cross-sectional. Therefore, although we have interpreted the data to mean that central arterial stiffening is causatively related to IHD, we cannot affirm the causal relationship. Third, the two groups with and without IHD differed in age, gender, smoking, duration of diabetes mellitus, and other characteristics that may have affected the results. However, we employed multivariate analyses as shown in **Tables 2 and 3** to statistically adjust for these possible confounders, and showed the independent association between IHD and aortic stiffness.

In conclusion, diabetic patients with IHD have increased stiffness of arteries, especially of the aorta. This finding supports the concept that central arterial stiffness plays an important role in the development of IHD.

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