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Left Ventricular Hypertrophy is Unrelated to Pulse Wave Velocity in Type 2 Diabetic Patients

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Summary. **Objective: Left ventricular hypertrophy (LVH) has been identified as an independent risk factor for cardiovascular diseases in diabetic patients. Pulse wave velocity (PWV) is a noninvasive method for assessing atherosclerosis, and there have been many recent reports on the relationship between PWV and cardiovascular diseases. The aim of this study was to assess the association between PWV and LVH in diabetic patients. Patients and Methods: Forty-three outpatients with type 2 diabetes participated in the study. The left ventricular mass index (LVMI) was determined by echocardiography, while the brachial-ankle PWV (baPWV) was measured using a recently developed device (ABI/PWV). Results: There was no significant correlation between mean baPWV and LVMI in diabetic patients (r=0.05, 0= 0.756) using univariable analysis. Multiple regression analysis showed that the effect of mean baPWV to LVMI was also not significant, even when controlled by compounding factors, and was shown to be much weaker than the effects of systolic blood pressure (SBP), body mass index (BMI), and nephropathy. Conclusion: Mean baPWV was less of an influence on LVH than BMI, SBP, or diabetic nephropathy in type 2 diabetic patients. In diabetes, non-haemodynamic factors might play a greater role in the pathogenesis of LVH than haemodymanic factors.**

Key words — PWV, LVH, type 2 diabetes.

INTRODUCTION

Cardiovascular diseases are major causes of morbidity and mortality in patients with type 2 diabetes mellitus[1]. This is particularly pronounced in type 2 diabetic patients with elevated urinary albumin excretion[2]. Abnormalities in well-established cardiovascular risk factors (e.g. dyslipidemia, arterial hypertension, smoking, glycemic control, and body mass index(BMI)) cannot fully account for this finding[3,4]. Left ventricular hypertrophy (LVH) has been identified as an independent risk factor for cardiovascular diseases (CVD) in patients with diabetes[5] as well as in the general population[6,7].

Arterial stiffness increases with age[8] and hypertension[9], and is also enhanced in diabetic patients[10]. The most obvious consequences of arterial stiffening are increased pulse pressure caused by higher systolic blood pressure (SBP) and lower diastolic blood pressure (DBP), resulting in increased left ventricular afterload and altering coronary perfusion[9,10]. Thus, high arterial stiffness in diabetes may be one cause of LVH through increased left ventricular afterload. Arterial stiffness can be assessed noninvasively by measuring the pulse-wave velocity (PWV)[8,11]. Several reports have indicated that atherosclerosis first develops in the aorta and then in the cerebral and coronary arteries[12, 13]. PWV has therefore been reported to be a useful method for assessing early-stage atherosclerosis. It has been reported that PWV

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Abbreviations—BMI, body mass index; CVD, cardiovascular disease; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; PWV, pulse wave velocity; SBP, systolic blood pressure.

constitutes a forceful maker of cardiovascular risk in hypertensive patients[14]. In this study, we investigated the relationship between PWV and LVH in patients with type 2 diabetes mellitus.

PATIENTS AND METHODS

Subjects

Outpatients with type 2 diabetes mellitus (according to World Health Organization criteria) were recruited at Niigata University Hospital. Exclusion criteria were as follows: type 2 diabetes for <1 year, history of myocardial infarction, history of angina as defined by the Rose questionnaire[15], an abnormality of segmental wall motion in the left ventricle as seen on echocardiography, heart failure, uncontrolled hypertension (blood pressure >180/100 mmHg), significant aortic stenosis, known serious arrhythmia, atrial fibrillation, left bundle branch block, previous coronary artery bypass surgery, treatment with digoxin, and severe, chronic, or acute illness. All patients provided informed consent.

Echocardiography

Echocardiography was performed according to the recommendations of the American Society of Echocardiography[16] using a Hewlett Packard SONOS 2500 equipped with a 2.5 MHz transducer. The M-mode echocardiogram was guided by a two-dimensional image in the parasternal long axis view. The following variables were measured: left ventricular end-diastolic diameter (LVDD) and end-systolic diameter (LVSD), and ventricular septal thickness (STD) and posterior wall thickness in the diastole (PWTD). Left ventricular mass was calculated according to Penn's formula: $1.04[(STD+LVDD+PWTD)^3-(LVDD)^3]-13.6$[17]. The left ventricular mass index (LVMI) was calculated by dividing LVM by the body surface area (g/m^2). The body surface area was calculated according to the Dubois formula $[0.0001\times71.84\times(\text{weight in Kg})^{0.425}\times(\text{height in cm})^{0.275}]$.[18] Wall motion was analyzed in the 16 segments of the left ventricle as defined by the American Society of Echocardiography.[16] All measurements were averaged over 5 cycles. Intraobserver error was < 5%.

Clinical measurements

SBP, DBP, BMI, and levels of HbA1c were measured in all patients. The presence of diabetic retinopathy, determined by fundus photography following pupillary dilatation, was graded as nil, simple, or proliferative. Regarding diabetic nephropathy, patients were divided into three groups according to the degree of albuminuria. A timed overnight urinary albumin excretion rate of less than 10 μg/min, that of 10-200 μg/min, and that of more than 200 μg/min were defined as normoalbuminuria (N), microalbuminuria (M1), and macroalbuminuria (M2), respectively. Bilateral brachial-ankle PWV (baPWV) was measured in all patients using a new device, ABI/PWV (BP-203RPE; Nihon Colin). The baPWV measurement was performed according to the standard method [19]. Fig. 1 shows the relationship between the left and right baPWV. Since there was a significant positive correlation between the left and right baPWV (r= 0.926, p<0.0001), we used the mean right/left baPWV value during analysis.

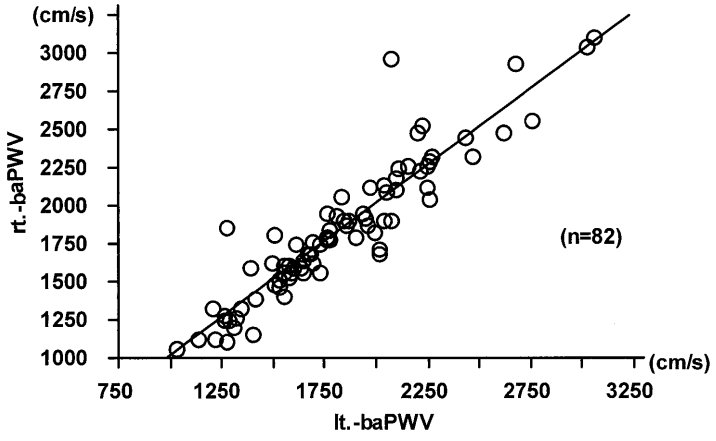

Fig 1. Correlation between left (lt.) and right (rt.) baPWV. There was a significant positive correlation between left and right baPWV (r=0.926, p < 0.0001).

Table 1. Clinical characteristics of 43 type 2 diabetic patients

Number	43
LVMI (g/m²)	114.0 ± 24.5
Mean-baPWV(cm/s)	1941 ± 458
Sex (M/F)	(24 / 19)
Age (years)	64.2 ± 7.6
Known diabetes duration (years)	14.8 ± 8.2
Body mass index (kg/m²)	23.6 ± 3.3
HbA1c (%)	7.2 ± 1.3
Treatment	
(Diet / SU / α GI / BG / Thiazolidine / Insulin)	(4 / 31 / 3 / 10 / 4 / 7)
Retinopathy	
(nil / simple / proliferative)	(26 / 6 / 11)
Nephropathy	
(N / M1 / M2)	(31 / 10 / 2)
Systolic blood pressure (mmHg)	139.5 ± 19
Diastolic blood pressure (mmHg)	80.8 ± 9.6
Previous antihypertensive treatment (%)	53.5
Duration of antihypertensive treatment (years)	9.2 ± 8.6
Number of treatments with ACE inhibitor	15
AT II R-blocker	13
β-blocker	1
calcium antagonist	14
diuretics	2
α-blocker	2

Data are means ± S.D. or n. SU, sulfonylurea; α GI, α glucosidase inhibitor; BG, biguanide. Timed overnight urinary albumin excretion of less than 10μg/min, that of 10-200 μg/min, and that of more than 200 μg/min were defined as normoalbuminuria (N), microalbuminuria (M1) and macroalbuminuria (M2), respectively.

Table 2. Correlation coefficient of each variable with left ventricular mass index

Independent variables	r	P value
Sex (male=1/ female=0)	0.29 †	0.062
Age (years)	0.02	0.892
Known diabetes duration (years)	0.02	0.878
HbA1c (%)	0.05	0.732
Retinopathy (nil=1/simple=1/proliferative=2)	0.12†	0.448
Nephropathy (N=0/M1, M2=1)	0.414 †	0.006
Body mass index (Kg/m²)	0.21	0.187
Systolic blood pressure (mmHg)	0.18	0.256
Diastolic blood pressure (mmHg)	0.12	0.451
Mean blood pressure (mmHg)	0.15	0.324
Anti-hypertensive treatment (yes=1, no=0)	- 0.05 †	0.448
Mean baPWV (cm/s)	0.05	0.756

n=43; r, Pearson's correlation coefficient or Spearman's correlation coefficient.†

Table 3. Relationship of selected variables with left ventricular mass index in multiple regression models

	Model 1		Model 2		Model 3	
	β	p	β	p	β	p
Mean baPWV	0.06	0.682	- 0.12	0.523	- 0.15	0.475
Systolic blood pressure	0.24	0.121	0.29	0.147	0.30	0.145
Body mass index	0.29	0.065	0.24	0.116	0.25	0.116
Nephropathy (N=0, M1, M2=1)	0.43	0.005	0.35	0.021	0.35	0.031

β, standardized coefficient with left ventricular mass index; Models 1, controlled for age and sex; Models 2, controlled for age, sex, antihypertensive treatment, and all other variables in the table; Models 3, controlled for HbA1c and known diabetes duration in addition to variables in models 2.

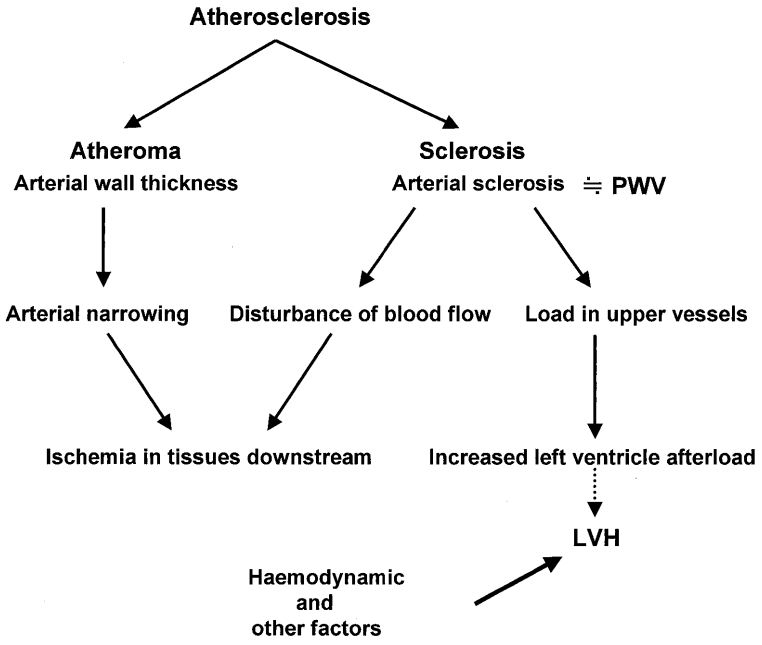

Fig 2. Schematic presentation of the association between atherosclerosis and left ventricular hypertrophy. Atherosclerosis consists of two separate and distinct conditions, ie., atheroma and sclerosis. Sclerosis causes dilation and stiffening with impaired compliance and with an increased load on the left ventricle upstream.

Statistical analysis

Values are presented as means ± standard deviation (S.D.). To evaluate the relation of baPWV and other factors to LVMI, Pearson's or Spearman's correlation analysis was applied, followed by multiple linear regression analysis. A P value of <0.05 was considered statistically significant. All calculations were made with commercially available software (SPSS 11.0 J for Windows, SPSS Inc).

RESULTS

Table 1 shows the characteristics of the 43 type 2 diabetic patients. The prevalence of diabetic retinopathy and nephropathy was 39.5% and 27.9%, respectively. The following factors were analyzed for the association with LVMI in the correlation coefficient: sex, age, known diabetes duration, HbA1c, stage of diabetic retinopathy, grade of diabetic nephropathy, BMI, SBP, DBP, mean BP, prevalence of anti-hypertensive treatment, and mean baPWV (Table 2). Only nephropathy significantly

correlated with LVMI. The relationship of 4 selected variables with LVMI in multiple regression models is shown in Table 3. In multiple linear regression analyses, mean baPWV was not found to be significantly related to LVMI, and the relation was shown to be much weaker than those of SBP, BMI, or nephropathy. In addition, the regression coefficient of mean baPWV became negative when other haemodynamic-related factors were entered into simultaneous models as shown in models 2 and 3. Only nephropathy was significantly associated with LVMI in every multiple model.

DISCUSSION

We measured left ventricular mass index and PWV in diabetic patients. Higher LVMI was associated with an increased prevalence of CVD and many of its known risk factors. Higher PWV was also associated with an adverse CVD risk factor profile.

The mechanism underlying the relationship between LVH and CVD is not clear. It has been suggested that LVH increases myocardial oxygen demand and coronary vascular resistance[20], decreases coronary blood flow reserve[21], and increases the incidence of ventricular arrhythmias[22].

One of the contributions to LVH is atherosclerosis. Atherosclerosis causes a cardiovascular load in the upper vessels, and this then increases left ventricle afterload. LVH is thought to be the product of this afterload.

PWV that indicates arterial stiffness is strongly associated with both the presence and the extent of atherosclerosis. In fact, it has been reported that the more advanced the atherosclerosis, the higher the PWV value[14].

This study was undertaken to identify whether there is a relationship between LVH and PWV in type 2 diabetic patients. Contrary to expectations, the present study showed that LVMI was less correlated with mean baPWV than SBP, BMI, or diabetic nephropathy. In addition, the coefficient of mean baPWV became negative when other related factors were entered into simultaneous models as shown in models 2 and 3. Accordingly, even if a patient were further investigated, the likelihood that a significant positive relationship between mean baPWV and LVMI could be found is remote. There are very few reports that have examined the relationship between the two factors. Only one paper has reported that cardiac hypertrophy was positively correlated with aortic PWV in twenty hypertensive patients, even when corrected for age[23]. However, this correlation disappeared when systolic pressure was entered into the equation; thus, these findings, adjusted for age and blood pressure, support our study. Fig. 2 shows the schematic presentation of the association between atherosclerosis and left ventricular hypertrophy. Atherosclerosis consists of two separate and distinct conditions, ie., atheroma and sclerosis. Sclerosis causes dilation and stiffening with impaired compliance and with an increased load on the left ventricle upstream. Based on the results of our study, the sclerosis factor is not likely to be a major contributor to the etiology of LVH.

The pathogenesis of LVH appears to be multifactorial, but it can be divided into two major categories: haemodynamic and non-haemodynamic[24]. Haemodynamic factors, mainly high blood pressure, are the major cause in non-diabetic subjets. However, SBP was less associated with LVMI than BMI or diabteic nephropathy in the present study. Thus, non-haemodynamic factors seem to play a greater role in the etiology of LVH than haemodynamic factors in diabetes although the number of subjets in the present study was too small to reach a firm conclusion.

In summary, our results demonstrated that mean baPWV was less of an influence on LVH than BMI, SBP, or diabetic nephropathy in type 2 diabetic patients. In diabetes, non-haemodynamic factors might play a greater role in the pathogenesis of LVH than haemodymanic factors.

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