Original Article

Relation among Left Ventricular Mass, Insulin Resistance, and Hemodynamic Parameters in Type 2 Diabetes

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Increased left ventricular mass (LVM) is an independent cardiovascular risk marker, which often occurs independently of arterial blood pressure in type 2 diabetes. To investigate the factors related to the disproportionate increase in LVM in type 2 diabetes, we conducted a cross-sectional study. We studied 40 male type 2 diabetic patients aged 36 to 70 years with controlled blood pressure. Magnetic resonance imaging was used to measure LVM accurately. Radial arterial waveforms were recorded non-invasively by applanation tonometry to assess the hemodynamic status, radial augmentation index (AI) and time from forward peak to reflection peak (TPP). Glycemic control status and insulin resistance were evaluated by plasma HbA1c and homeostasis model assessment (HOMA) score, respectively. *E*/*E′*, an echocardiographic parameter for left ventricular (LV) diastolic function, was also analyzed by echocardiography. Univariate analyses showed that HbA1c and TPP had trends toward a positive correlation with LVM indexed for body surface area (LVMI), whereas AI did not. When patients' age, heart rate, and systolic blood pressure were simultaneously included in the linear regression model, the TPP and HOMA score were independently related to LVMI ($p<0.05$ for each variable). Increased LVMI was accompanied with impaired LV diastolic function assessed by *E*/*E′*. In conclusion, the TPP and HOMA score were associated with a modest but clinically relevant increase in LVM in type 2 diabetes independently of arterial blood pressure. Pulse wave analysis may reveal hemodynamic alterations that affect LVM but that cannot be identified using a sphygmomanometer. (*Hypertens Res* 2008; 31: 425–432)

***Key Words*: left ventricular hypertrophy, diabetes mellitus, insulin resistance, pulse wave analysis, diastolic dysfunction**

Introduction

Cardiovascular events are common causes of morbidity and mortality in patients with diabetes (*1*). A disproportionate increase in left ventricular (LV) mass (LVM) is one of the common features of diabetic heart disease, and may serve as an ideal risk marker and target for treatment to reduce cardiac events in diabetes (*2*, *3*).

The mechanism responsible for the increase in LVM in diabetic patients has not been clarified. In general, hemodynamic as well as non-hemodynamic factors influence the development of LV hypertrophy (LVH) (*4*). Diabetes is associated with increased arterial stiffness when the effect of arterial pressure is corrected for (*5*, *6*), and an increase in arterial stiffness deteriorates hemodynamic status probably *via* its effects

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on reflected pulse waves (*7*). Glycemic control status and insulin resistance may stimulate LVH by promoting arteriosclerosis and increasing arterial stiffness as well as by direct, arterial pressure–independent effects on cardiac myocytes (*3*, *8*). Thus, LVH could arise from a deterioration of hemodynamic status, glycemic control status, and/or insulin resistance in diabetic patients.

In this study, we investigated the associations of hemodynamic parameters assessed by both pulse wave analysis and metabolic parameters with LVM indexed for body surface area (LVMI) in type 2 diabetes. In addition, the association of LVMI with LV diastolic function was also analyzed to study the impact of a modest increase in LVM on cardiac function.

Methods

Study Population

Forty male patients with type 2 diabetes ranging in age from 36 to 70 years were recruited consecutively from an outpatient department at Kyoto University Hospital and from general practitioners in Kyoto. We analyzed only male patients, since a large gender difference in AI has previously been reported and the menstrual cycle or menopause may affect arterial stiffness (*9*). Type 2 diabetes was diagnosed based on the diagnosis and classification of diabetes mellitus of the expert committee (*10*). Patients with significant arrhythmias, old myocardial infarction, LV systolic dysfunction, valvular heart disease, overt heart failure, overt renal failure, aortic or peripheral disease, cerebrovascular disease, or contraindication for MRI were excluded. In addition, patients with insulin therapy were excluded, because the assessment of insulin resistance would be complicated in these patients (*11*). We included both hypertensive and normotensive patients if their blood pressure was controlled to less than 140/90 mmHg on repeated measurements on two or more different visits, and the status of antihypertensive medication was recorded.

This study was approved by the Institutional Review Board of Kyoto University Graduate School of Medicine, and written informed consent was obtained from each patient. The investigation conformed to the principles outlined in the Declaration of Helsinki.

Pulse Wave Analysis

Measurements were performed on the morning after a 12-h fast and 30 min of rest in a supine position in a quiet, temperature-conditioned room (26±2°C). Patients were not allowed to take tobacco, caffeine or medicine on the morning of the study. Hemodynamic status was assessed non-invasively with the commercially available applanation tonometry device HEM-9000AI (OMRON HEALTHCARE Co., Ltd., Kyoto, Japan). Peripheral pressure waveforms were recorded over 30 s from the radial artery at the wrist with the subject in a sitting position. Simultaneously, arterial blood pressure was measured at the opposite arm. The system software allowed online recording of the peripheral waveforms, which was assessed visually to ensure that the best possible recordings were obtained and that artifacts from movement were minimized. The peak point of the forward wave and reflected wave were automatically identified using fourth derivatives for each radial arterial waveform and averaged as previously described in order to measure the augmentation index (AI) and the time from forward peak to reflection peak (TPP) (Fig. 1) (*12*). AI was defined as a percentage as follows: $AI = B/A \times 100$, where A is the amplitude of the forward traveling wave and B is the amplitude of the reflected wave. As AI is influenced by the heart rate, an index normalized for a heart rate of 75 bpm (AI@75) was calculated in accordance with Wilkinson *et al*. (*13*). TPP represents the travel time of the pulse wave to the peripheral reflecting site and back. The reproducibility and reliability of pulse wave analysis by HEM-9000AI have been reported previously (*14*).

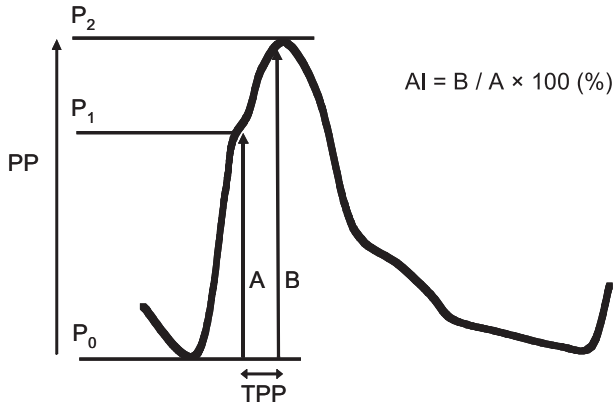

Fig. 1. *Definition of the indexes of arterial stiffness. A radial artery pressure waveform from a middle-aged man. P_1 is the pressure of the forward wave, P_2, coinciding with systolic blood pressure (SBP) in this case, is the pressure of the forward plus the reflected wave, and P_0 is diastolic blood pressure (DBP). PP, pulse pressure. The augmentation index (AI) is defined as the percent ratio of the amplitude of the reflected wave (B: $P_2 - P_0$) to the amplitude of the forward traveling wave (A: $P_1 - P_0$). The time from forward peak to reflection peak (TPP) is defined as the time interval between the peak point of the forward wave and the peak point of the reflected wave.*

Blood Sample Analysis

Each blood sample was collected by venipuncture just after the pulse wave analysis. Plasma was prepared by centrifugation of the blood samples and HbA1c was measured to assess glycemic control status. Insulin resistance was assessed by the previously validated homeostasis model assessment (HOMA) score, which was calculated using the formula: fast-

Table 1. Characteristics of Study Patients (n=40)

	Mean±SD (median)	Range
General characteristics		
Age, years	59.9±7.1 (60.0)	36–70
Height, m	1.68±0.07 (1.68)	1.54–1.81
Weight, kg	69.2±10.0 (66.0)	51–88
Body mass index, kg/m^2	24.5±3.1 (24.4)	19.0–31.2
Duration of diabetes, years	6.5±7.1 (4.0)	0.5–31.0
Duration of antihypertensive treatment, years (n=28)	12.4±10.0 (10.0)	0.5–30.0
Blood sample analyses		
Fasting blood glucose, mg/dL	113.8±25.5 (127.0)	101–219
Fasting IRI, μU/mL	6.6±4.1 (5.0)	1.3–19.4
HbA1c, %	6.8±0.9 (7.0)	5.0–8.8
HOMA score, U	2.2±1.5 (1.6)	0.4–6.3
Creatinine, mg/dL	0.8±0.17 (0.8)	0.5–1.2
BNP, pg/mL	18.7±14.1 (15.0)	2.7–61.1
Blood pressure		
Systolic blood pressure, mmHg	132±15.6 (135)	86–158
Diastolic blood pressure, mmHg	78±10.7 (78)	55–97
Mean blood pressure, mmHg	96±11.1 (97)	65.3–114.7
Pulse pressure, mmHg	54±12.4 (54)	31–91
Pulse wave analysis		
Heart rate, bpm	63±10.0 (59)	48–93
AI, %	84.1±11.1 (85.0)	55.0–110.0
AI@75, %	79.1±10.1 (79.6)	48.2–103.2
TPP, ms	123.4±17.7 (124.0)	86.0–154.0
Echocardiographic profiles		
Left ventricular end diastolic dimension, mm	48.8±3.8 (49.0)	40.0–56.0
Ejection fraction (Teichholz formula), %	64.8±7.3 (64.5)	47.0–79.0
Interventricular wall thickness, mm	9.1±1.3 (9.0)	7.0–12.0
Posterior wall thickness, mm	9.3±1.4 (9.0)	7.0–13.0
Left ventricular mass (Penn method), g	191.3±45.4 (180.7)	114.0–293.7
LVMI (Penn method), g/m^2	106.7±22.4 (104.3)	66.3–150.4
E/E'	8.8±2.5 (9.0)	4.9–17.2
MRI profiles		
Left ventricular end diastolic volume, mL	123.6±24.6 (129.3)	71.9–179.1
Left ventricular end systolic volume, mL	47.6±14.0 (48.1)	17.6–74.5
Ejection fraction (Simpson method), %	61.9±7.4 (61.3)	50.4–79.6
Left ventricular mass (Simpson method), g	127.2±30.2 (118.2)	80.9–251.2
LVMI (Simpson method), g/m^2	70.9±14.4 (69.2)	48.4–126.2

IRI, immunoreactive insulin; HOMA score = fasting blood glucose (mg/dL)/18 × fasting IRI (μU/mL)/22.5; BNP, brain natriuretic peptide; AI, augmentation index; AI@75 = AI + 0.44 × (heart rate − 75); TPP, time from forward peak to reflection peak; LVMI, left ventricular mass index; E/E', ratio of mitral velocity to early diastolic velocity of the mitral annulus.

ing insulin (μU/mL) × fasting glucose (mmol/L)/22.5 (*11*). Factors potentially associated with an increase in LVM, such as plasma brain natriuretic peptide (BNP) concentrations, were also analyzed (*15*).

Assessment of LVM

Patients underwent MRI for precise assessment of LVM. MRI was performed with a 1.5-T whole-body imager (Symphony; Siemens, Erlangen, Germany), with multiple surface coils connected to phased-array receivers. MRI were analyzed by an experienced radiologist without any clinical information but with the aid of commercially available software (Argus; Siemens). End-diastolic volume, end-systolic volume, and LVM were calculated on the basis of the Simpson rule. LVM was calculated as a product of the specific gravity of the myocardium (*i.e.*, 1.05 g/cm^3) and integrated LV myocardial area (*16*). LVM was measured on both end-

diastolic images and end-systolic images, and the mean of the two measurements in systole and diastole was used for data analysis. LVMI was calculated as LVM divided by body surface area.

In addition, as there is no established normal range of LVM measured by MRI, echocardiographic measurement of LVM was also performed to define the normal range of LVM. Echocardiography was performed on each patient by two expert sonographers with a Phillips Sonos 5500 (Phillips, Bothell, USA). Echocardiographic images were either recorded on videotapes or directly stored in digital form on a hard disk drive. Two-dimension guided M-mode tracings were analyzed by two independent observers who were unaware of the subject's MRI data to calculate LVM using the Penn formula (*17*). We defined LVH as echocardiographic LVMI >134 g/m^2 based on the Penn formula (*17*). LV ejection fraction was estimated using the Teichholz formula (*18*). Two-dimensional and color Doppler imaging were performed to rule out valvular heart disease and wall motion abnormality. The data acquisition by each modality was performed within 2 weeks from pulse wave analysis.

Assessment of LV Diastolic Function

At echocardiography, each patient underwent tissue Doppler analysis of medial mitral annulus in the apical 4-chamber view, and the ratio of trans mitral blood flow velocity to early diastolic velocity of the mitral annulus (E/E') was calculated. The E/E' ratio has been utilized to estimate LV filling pressure and to evaluate myocardial relaxation. An $E/E' <10$ indicates normal diastolic function to mild diastolic dysfunction and an $E/E' \geq 10$ indicates moderate to severe diastolic dysfunction (*19*).

Statistical Analysis

Demographic data are presented as the means±SD and median. We examined the relation between echocardiographic LVM and LVM assessed by MRI by Pearson correlation. Univariate associations between LVMI measured by MRI and clinical variables were assessed using Pearson or Spearman correlations, based on the distribution of variables.

Variables of $p<0.1$ were used as potential independent variables in a multivariate linear regression model. Because the systolic blood pressure, glycemic control status, and insulin resistance of patients have been reported to have a significant correlation with LVMI, these parameters were simultaneously included in the linear regression model. We also included the age and heart rate of patients, because these parameters were reported to have significant associations with the results of pulse wave analysis (*13*). We developed a multivariate linear regression model using these potential variables and predetermined covariates.

In addition, we assessed the association between LVMI and E/E' using Spearman correlation to investigate the effect of increased LVM on LV diastolic function. p values <0.05 were considered statistically significant. Data were analyzed with JMP IN 5.1.1 software.

Table 2. Univariate Relations of LVMI to Hemodynamic Parameters and Other Potential Factors

Variables	*r*	*p* value
Age	0.14	0.360
Fasting blood glucose	−0.08	0.629
HbA1c	−0.27	0.089
HOMA score	0.17	0.289
BNP	0.15	0.365
Heart rate	−0.26	0.101
Systolic blood pressure	0.05	0.750
Diastolic blood pressure	0.13	0.416
Pulse pressure	0.21	0.192
AI	0.03	0.824
AI@75	−0.08	0.630
TPP	−0.29	0.065

LVMI, left ventricular mass index; HOMA score = fasting blood glucose (mg/dL)/18 × fasting IRI (μU/mL)/22.5; BNP, brain natriuretic peptide; AI, augmentation index; AI@75 = AI + 0.4 × (heart rate − 75); TPP, time from forward peak to reflection peak; IRI, immunoreactive insulin.

Results

Characteristics of Study Patients

The characteristics of the 40 study patients are shown in Table 1. The mean duration of diabetes in this group was 6.4 years. Glycemic control was maintained by oral antidiabetic drugs (24 patients), or by diet and exercise only (16 patients). Among the 40 patients, 28 were receiving antihypertensive medications or vasodilators. These included angiotensin-converting enzyme inhibitors ($n=3$), angiotensin II receptor blockers ($n=14$), β-blockers ($n=9$), calcium channel blockers ($n=18$), diuretics ($n=1$), and nitrates ($n=4$). Seventeen subjects were receiving lipid-lowering drugs. The mean HbA1c of the patients was 6.8% and the mean HOMA score was 2.2. Although patients did not take their medicine on the day of the arterial pulse wave data and blood sample collection, the blood pressure at pulse wave analysis was within normal range in most patients. Heart rate, AI and TPP were widely distributed in our diabetic patients.

LVM Measured by Echocardiography or MRI, and Evaluation of LVH

Echocardiographic and MRI data are also shown in Table 1. There was a good correlation between echocardiographic LVM and LVM measured by MRI ([LVM measured by MRI] = [LVM measured by echocardiography] × 0.487 +

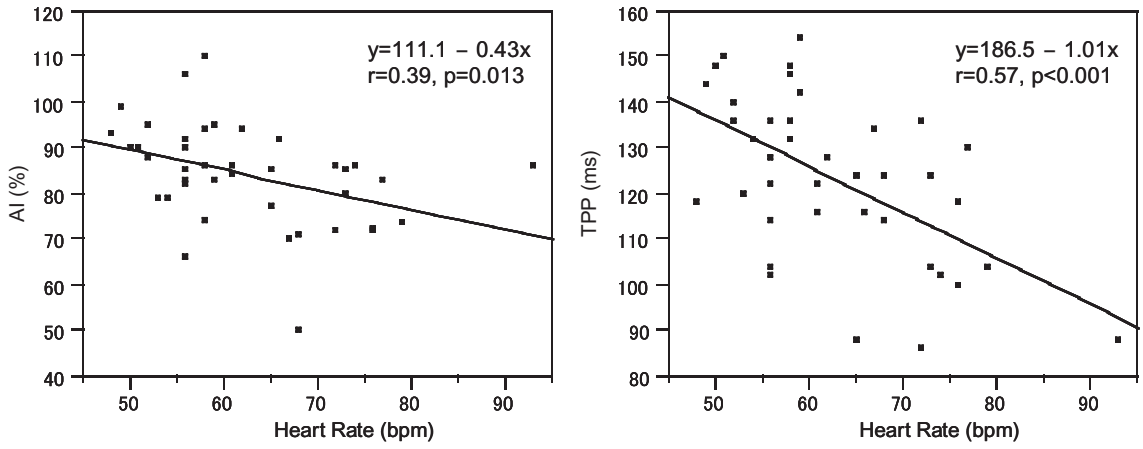

Fig. 2. *Associations between augmentation index (AI) or time from forward peak to reflection peak (TPP) and heart rate. Significant inverse correlations of AI and TPP to heart rate were observed.*

34.1, $r=0.73$, $p<0.0001$). Echocardiography overestimated LVM relative to MRI, which was compatible with previous reports. Mild LVH was present in 6 of the 40 patients (15%).

Associations of Hemodynamic Parameters, Insulin Resistance and Other Variables with LVMI

Univariate analyses showed that HbA1c and TPP had trends toward correlations to LVMI measured by MRI ($0.05<p<0.1$). In contrast, we found no relation between AI and LVMI. After adjusting for the heart rate differences, there was still no association between AI@75 and LVMI. We found no significant associations among the included variables, including age, blood pressure, pulse pressure, BNP and LVMI (Table 2). There were also no significant correlations between HbA1c and AI or TPP, and between HOMA score and AI or TPP (data not shown). Significant inverse correlations of AI and TPP to heart rate were observed (Fig. 2).

When potential independent variables, *i.e.*, age, heart rate, HOMA score, and systolic blood pressure, were simultaneously included in the linear regression model, the TPP and HOMA score were independently related to LVMI ($p<0.05$ for each variable) (Table 3). To evaluate the robustness of the multivariate model, we added the pulse pressure and the antihypertensive therapy to the model. The strong association between TPP or HOMA score and LVMI remained stable ($p<0.05$).

Association of LVM and LV Diastolic Function in Diabetic Patients with No or Mild LVH

To test whether an increase in LVM is associated with LV diastolic dysfunction in the normal to mildly increased range, we compared E/E', an echocardiographic parameter of diastolic function, with LVMI measured by MRI. The results indicated that E/E' was positively associated with LVMI ($r=0.38$, $p=0.016$). Thus, a relatively low-level increase in LVM was accompanied by LV diastolic dysfunction in our diabetic patients.

Table 3. Multivariate Analysis of Determinants of LVMI

Variables	β	SEM	p value
Age	0.148	0.274	0.592
Heart rate	−0.795	0.274	0.003
Systolic blood pressure	0.171	0.133	0.210
TPP	−0.456	0.143	0.003
HOMA score	3.318	1.371	0.030
HbA1c	−2.721	2.234	0.232

LVMI, left ventricular mass index; HOMA score = fasting blood glucose (mg/dL)/18 × fasting IRI (μU/mL)/22.5; TPP, time from forward peak to reflection peak; IRI, immunoreactive insulin.

Discussion

In the present study, we observed a significant and independent association between TPP or HOMA score and LVMI in type 2 diabetic patients with controlled blood pressure. Furthermore, a relatively low-level increase in LVM was also associated with the development of LV diastolic dysfunction.

We evaluated hemodynamic status using two parameters, AI and TPP, in this study. We found a significant inverse correlation of TPP with LVMI, although there was no significant relation between AI and LVMI. AI is primarily determined by both the intensity and the timing of reflected pressure waves (*20*). The intensity of wave reflection will depend on the serial distribution of vascular diameter and the tonus of small muscular arteries at the major site of pressure wave reflection. In contrast, TPP is defined only by the relationship of the timings of the forward wave peak and the reflection wave peak; therefore, AI could evaluate the sum of organic and functional

changes of the arterial tree, while TPP could evaluate mainly organic changes of stiffness in the elastic arteries. As most of our patients were receiving vasoactive drugs (28/40), alterations in the tonus of small muscular arteries might occur in such patients and significantly influence AI but not TPP. In addition, although increased AI has been demonstrated in diabetes (*5*, *6*), some investigators have contradicted the relation between diabetes and elevated AI (*21*). Instead, they reported deterioration of other parameters, *i.e.*, arterial stiffness, pulse wave velocity and time to the foot of the reflected wave (T_r), in patients with diabetes (*21*). These reports imply our finding of a discrepancy between TPP and AI in the evaluation of hemodynamic status, and call into question the validity of AI as a useful index of hemodynamic status in diabetes.

A strong correlation between HOMA score and LVMI was observed in this study in accordance with previous reports. The Framingham Heart Study indicated a positive correlation of HOMA score to LVM in female subjects, but not in male subjects (*3*). On the other hand, Shigematsu *et al*. reported an association of insulin resistance with an increase of LVM in male hypertensive patients (*22*). In their study, however, the subjects differed in race and other background characteristics. The Framingham Heart Study is a population-based large cohort study, and the majority of its subjects are Caucasians, while the present study and the study by Shigematsu *et al*. (*22*) are small studies employing Japanese patients. These differences might, in part, explain the discrepancy in regard to sex-related differences in the relation of insulin resistance to an increase in LVM.

Insulin resistance can cause the development of LVH *via* direct and indirect mechanisms, including lipotoxicity, glucotoxicity, the direct hypertrophic action of increased insulin on cardiac myocytes, promotion of matrix remodeling, sympathetic activation, and an increase in renal sodium re-adsorption (*23*). Some of these actions may also promote arteriosclerosis and an increase in arterial stiffness, and thereby secondarily stimulate LVH. Angiotensin II is one of the possible mediators of insulin resistance–induced deterioration of cardiovascular morphology and function. Insulin resistance up-regulates the number and activity of angiotensin II type 1 receptors (AT1R) (*24*). Mitogenic effects of angiotensin II *via* AT1R on vascular smooth muscle cells can promote arterial hypertrophy and increase arterial resistance, resulting in LVH (*25*). Angiotensin II also directly stimulates LVH by a signal *via* AT1R on cardiac myocytes (*26*). An increase in myocardial oxidative stress may partly mediate the hypertrophic action of angiotensin II (*27*). Thus, insulin resistance is closely associated with augmented effects of angiotensin II. Indeed, AT1R blockers ameliorate both LVH and insulin resistance (*28*). The association between HOMA score and LVMI seen in this study was independent of the parameters of hemodynamic status TPP and AI, which suggested that direct, hemodynamic-independent effects of insulin resistance on the myocardium might play a significant role in the development of LVH in type 2 diabetes.

We also found that heart rate was inversely associated with LVMI. Although not widely acknowledged, the existence of a significant correlation of heart rate to LVM has been suggested by previous studies (*29*, *30*). Our findings appear to confirm these reports. Although a univariate analysis showed only weak association between TPP and LVMI, a multivariate analysis including heart rate as a covariate indicated a significant correlation between these two parameters. This might have resulted from the inverse association between TPP and heart rate, and the heart rate should act as a negative confounder on the association of TPP and LVMI in our multivariate model.

LVMI were relatively smaller and the proportion of patients with LVH was also smaller in our patients (15%) than in previous reports in diabetic patients (32% to 44%) (*31*). Nevertheless, the clear positive correlation between LVMI and the E/E' ratio observed in our patients suggested that only a modest increase in LVM could impair LV diastolic function in type 2 diabetes. As LV diastolic dysfunction often causes decompensated heart failure in the absence of systolic dysfunction in diabetic hearts (*32*), the detection of diastolic dysfunction in diabetic patients without significant LVH is important to prevent cardiovascular events.

The present study is also unique in its use of MRI for accurate measurement of LVMI. The greater accuracy and reproducibility of MRI enables us to detect relatively small but significant differences in LVM using a smaller sample size in group analyses (*33*). As accurate measurement of LVM by echocardiography or by MRI is time- and cost-consuming and requires skilled operators, it is arduous to use such methods to screen diabetics for patients at high risk for cardiovascular events. Thus, simple and reliable prescreening methods that can identify diabetic patients who are likely to have LVH and at high risk for cardiovascular events may be needed before the precise evaluation of LVM by echocardiography or MRI. Because TPP indicated a significant correlation to LVMI, assessment of hemodynamic alterations by TPP may be valuable as one of such prescreening methods to identify a high risk subgroup among patients with type 2 diabetes.

Several limitations should be noted in the interpretation of the study results. First, the small number of study subjects might limit the strength of our conclusions. Although the final model showed a significant association between TPP or HOMA score and LVMI, the multivariate model with 6 variables might be overloaded (*34*). Second, we included patients under medical therapy in the study, because the results should be applicable to routine clinical practice. The rationale for this design is that most diabetic patients will take multiple drugs during follow up, and prescreening methods stratifying the cardiovascular risk of such patients should be introduced into clinical practice; however, the effects of the drugs might make scientific interpretation of the results arduous.

In conclusion, TPP and HOMA score were associated with a modest but clinically relevant increase in LVM in patients with type 2 diabetes independently of arterial blood pressure.

Pulse wave analysis may reveal hemodynamic alterations that affect LVM but that cannot be identified by a sphygmomanometer.

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