Original Article

Left Ventricular Diastolic Dysfunction as Assessed by Echocardiography in Metabolic Syndrome

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The purpose of the present study was to elucidate the cardiac structure and function in patients who have metabolic syndrome but no history of cardiovascular disease by analyzing echocardiographic findings. Echocardiographic examination was performed to screen for cardiovascular disease in 135 patients who were in their sixties. Patients were divided into metabolic syndrome ($n=65$, age: 65 ± 2.7 years) and non-metabolic syndrome ($n=70$, age: 66 ± 2.5 years) groups based on the criteria for metabolic syndrome proposed by the Japanese Society of Hypertension and seven other societies in 2005. The left ventricular (LV) wall thickness and dimension were measured by M-mode echocardiography. The relative wall thickness, LV mass index, and LV ejection fraction (LVEF) were calculated. LV diastolic function was assessed by the peak velocity of early rapid filling (E velocity) and the peak velocity of atrial filling (A velocity), and the ratio of E to A (E/A) was assessed by the transmitral flow. The Tei index, which reflects both LV diastolic and systolic function, was also calculated. There were no differences in relative wall thickness, LV mass index, or LVEF between the two groups. However, both the E/A and Tei index were significantly different between the metabolic syndrome (0.66 ± 0.14 and 0.36 ± 0.07 , respectively) and non-metabolic syndrome (0.88 ± 0.25 and 0.29 ± 0.09) groups ($p<0.001$). These results indicate that patients with metabolic syndrome can have cardiac diastolic dysfunction even if they have neither LV hypertrophy nor systolic dysfunction. (*Hypertens Res* 2006; 29: 897–903)

Key Words: metabolic syndrome, cardiac function, echocardiography

Introduction

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for chronic heart failure published in 2005 regard patients with metabolic syndrome as stage A patients who are at high risk for heart failure but without structural heart disease (1). Because metabolic syndrome is recognized as raising the risk of cardiovascular disease (2–6), patients with metabolic syndrome are thought to have a high risk of heart failure, which is caused by cardiovascular events such as myocardial infarction. However, consensus is

still lacking in regard to the cardiac function of patients with metabolic syndrome without structural heart disease. Therefore, the purpose of the present study was to clarify the cardiac function of patients with metabolic syndrome who have no history of cardiovascular disease.

Methods

Subjects and Protocol

One hundred and thirty-five consecutive patients who were in their sixties and diagnosed as having atherosclerosis-related

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diseases at Sakaide Municipal Hospital were entered in the present study from April 2004 to the end of March 2006. Atherosclerosis-related diseases included hypertension, diabetes mellitus, and dyslipidemia, which were diagnosed according to the guidelines of the Japanese Society of Hypertension (7), the Japan Diabetes Society (8), and the Japan Atherosclerosis Society (9). Informed consent was obtained from all of the participants. None of the subjects had a history of any atherosclerotic cardiovascular diseases or stroke. Blood pressure was determined in the outpatient clinic using the conventional cuff method. An echocardiograph was performed to assess the cardiac function, and blood sampling was performed in the morning after a 12-h overnight fast. Levels of plasma total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, and fasting blood glucose were measured by standard laboratory techniques. The patients were divided into metabolic syndrome and non-metabolic syndrome groups based on the criteria proposed by the Japanese Society of Hypertension and seven other societies in 2005 (10). Sixty-five patients were diagnosed as having metabolic syndrome, and seventy patients were diagnosed as not having metabolic syndrome. The blood pressure, data for blood examination, and echocardiographic findings were compared between the two groups. This protocol was approved by the Ethical Committee of Sakaide Municipal Hospital.

Echocardiographic Examination

Two-dimensional and M-mode echocardiography was performed using an echocardiographic instrument (PowerVision 6000; Toshiba, Tokyo, Japan) with a 2.5-MHz transducer. We first measured the following left ventricular (LV) structural parameters by M-mode echocardiography: ventricular septal thickness (VS) at the chordae tendineae level, left ventricular end-diastolic dimension (LVDd), left ventricular end-systolic dimension (LVDs) at the chordae tendineae level, LV posterior wall thickness (PW) at the chordae tendineae level, dimensions of the ascending aorta (AO), and end-systolic dimension of the left atrium (LAD). We measured the LV septum and PW and LV cavity dimension by means of a leading-edge methodology according to the recommendations regarding quantitation in M-mode echocardiography by the American Society of Echocardiography (11). Whenever M-mode measurements were considered technically inadequate, two-dimensional measurements were performed using the American Society Echocardiography criteria (12). The LV mass was calculated according to the American Society of Echocardiography conventions (13) using the following equation: $LV\ mass = 0.80 [1.04 \times (PW + VS + LVDd)^3 - (LVDd)^3] + 0.6$. The LV mass index was calculated as the LV mass divided by the body surface area. Relative wall thickness, which increases with concentric remodeling and concentric hypertrophy, was calculated as $2 \times PW / LVDd$. The left ventricular ejection fraction (LVEF) was estimated by the modified Simpson method (14) and was used as the parameter

Fig. 1. Measurements of parameters of the left ventricular diastolic function and Tei index. E, peak early diastolic transmitral flow; A, peak late diastolic transmitral flow; E/A, the ratio of E to A; DcT, deceleration time of early diastolic transmitral flow. The Tei index is derived as $(a-b)/b$, where a is the interval between the cessation and onset of mitral inflow and b is the ejection time of LV outflow.

of LV systolic function.

We next measured the parameters of LV diastolic function by recording the LV diastolic inflow using pulsed Doppler echocardiography (15). The LV diastolic filling pattern was recorded from the apical transducer position with the sample volume situated between the mitral leaflet tips. The peak velocity of early rapid filling (E velocity) and the peak velocity of atrial filling (A velocity) were recorded, and the ratio of E to A (E/A) was calculated (Fig. 1, left). The deceleration time of the E velocity (DcT) was measured as the time interval from the E -wave peak to the decline of the velocity to baseline values. Because all subjects in the present study had a normal LV systolic function ($LVEF \geq 55\%$), no subject had a pseudonormal LV diastolic filling pattern (16).

Finally, we measured the Tei index, which reflects both LV systolic and diastolic function (17). Details of the method for measuring the Tei index have been published previously (18). The Tei index, defined as the sum of the isovolumic contraction time and isovolumic relaxation time divided by the ejection time, was obtained from Doppler recordings of LV inflow and outflow (Fig. 1). The Tei index is derived as $(a-b)/b$, where a is the interval between cessation and onset of mitral inflow, and b is the ejection time of LV outflow. In measuring a and b , we confirmed that the preceding RR intervals were the same in each patient.

Statistical Analysis

Data are expressed as the mean $\pm$ SD. Statistical analysis was performed using an SPSS software package (SPSS, Chicago,

Table 1. Comparison of Clinical and Ultrasonographic Variables between Non-Metabolic Syndrome and Metabolic Syndrome Patients

	Non-MS	MS	<i>p</i> value
Number (male/female)	70 (36/34)	65 (33/32)	—
Hypertension (% (No. of subjects))	51 (36)	54 (35)	NS
Diabetes mellitus (% (No. of subjects))	27 (19)	32 (21)	NS
Dyslipidemia (% (No. of subjects))	49 (34)	55 (36)	NS
Age (years)	66±2	65±3	NS
BMI (kg/m ²)	22.3±3.2	27.0±1.5	<0.001
Systolic BP (mmHg)	129±17	140±12	<0.001
Diastolic BP (mmHg)	73±9	77±8	0.003
Fasting blood glucose (mg/dl)	107±22	115±25	NS
Total cholesterol (mg/dl)	193±42	186±26	NS
HDL cholesterol (mg/dl)	57±17	52±10	NS
LDL cholesterol (mg/dl)	112±37	100±23	NS
Triglyceride (mg/dl)	110±59	159±58	<0.001
Echocardiographic parameters			
VS (mm)	9.9±1.9	10.8±1.4	0.002
PW (mm)	9.6±1.6	9.8±1.1	NS
RWT	0.43±0.08	0.42±0.07	NS
LVMI (g/m ²)	99±29	103±19	NS
LVEF (%)	65±5	64±4	NS
<i>E</i> (m/s)	0.62±0.16	0.55±0.15	0.007
<i>A</i> (m/s)	0.72±0.16	0.83±0.16	<0.001
<i>E/A</i>	0.88±0.25	0.66±0.14	<0.001
DcT (ms)	219±54	232±43	NS
Tei index	0.29±0.09	0.36±0.07	<0.001

Non-MS, non-metabolic syndrome; MS, metabolic syndrome; BMI, body mass index; BP, blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; VS, ventricular septal thickness; PW, posterior wall thickness; RWT, relative wall thickness; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; *E*, peak early diastolic transmitral flow; *A*, peak late diastolic transmitral flow; *E/A*, the ratio of *E* to *A*; DcT, deceleration time of early diastolic transmitral flow.

USA). An unpaired Student's *t*-test was performed to compare the variables between the metabolic syndrome and non-metabolic syndrome groups. Linear regression analysis was used to test the association between the cardiac function and the clinical parameters. Stepwise multiple regression analysis was performed to determine the correlation and independent variables for the *E/A* and Tei index. Values of *p*<0.05 were considered to indicate statistical significance.

Results

Clinical Characteristics in Metabolic and Non-Metabolic Syndrome Patients

The clinical characteristics of the patients with and without metabolic syndrome are summarized in Table 1. There were no differences in the prevalence of hypertension, diabetes mellitus, or dyslipidemia between the two groups. The body mass index (BMI), systolic and diastolic blood pressure

(SBP/DBP), and triglycerides were significantly higher in the metabolic syndrome patients than in the non-metabolic syndrome patients.

Comparison of Echocardiographic Parameters between Metabolic Syndrome and Non-Metabolic Syndrome Patients

The relative wall thickness and LV mass index were not significantly different between the patients with and those without metabolic syndrome (Table 1). The mean LVEF was normal and similar between the two groups (Fig. 2, left). However, *E* velocity was lower and *A* velocity was higher in the patients with metabolic syndrome than in those without it (Fig. 3). The *E/A* was lower in the patients with than in those without metabolic syndrome (Fig. 3). The Tei index was also higher in the patients with than in those without metabolic syndrome (Fig. 2, right).

Fig. 2. Comparison of LVEF and the Tei index between patients with and those without the metabolic syndrome. LVEF, left ventricular ejection fraction.

Assessment of the Clinical Parameters Related to E/A and the Tei Index

Linear regression analysis was performed to examine the relationship of E/A and the Tei index to clinical parameters in patients in both the metabolic syndrome and non-metabolic syndrome groups. The clinical parameters significantly associated with E/A and the Tei index are shown in Table 2. Both E/A and the Tei index correlated significantly with the clinical parameters that are included in the risk determinants of the criteria of metabolic syndrome, *i.e.*, SBP and DBP, fasting blood glucose, HDL cholesterol, and triglycerides. However, neither E/A nor the Tei index correlated with the parameters (total cholesterol and low density lipoprotein [LDL] cholesterol) that are not included in the risk determinants of the criteria of metabolic syndrome. A stepwise multiple regression analysis was performed to examine the clinical parameters that influence E/A and the Tei index. The results indicated that the triglycerides (β coefficient = -0.33 , $p < 0.001$) and SBP (β coefficient = -0.31 , $p < 0.002$) were independently associated with E/A (Table 3), and that fasting blood glucose (β coefficient = 0.33 , $p < 0.001$), BMI (β coefficient = 0.25 , $p = 0.002$), and triglycerides (β coefficient = 0.25 , $p = 0.002$) were independently associated with the Tei index (Table 4).

Discussion

This study compared the cardiac function between patients with and those without metabolic syndrome. These data lead us to the following conclusions: 1) the LVEF, which reflects LV systolic function, is preserved within normal limits for both metabolic syndrome and non-metabolic syndrome patients; 2) E/A , which reflects LV diastolic function, is more impaired in patients with metabolic syndrome than in patients without metabolic syndrome; 3) the Tei index, which reflects LV diastolic and systolic function, is more impaired in patients with than in those without metabolic syndrome; and 4) the clinical parameters (fasting blood glucose, triglycerides, and SBP) that are included in the criteria of metabolic

Fig. 3. Comparison of the parameters of left ventricular diastolic function between the patients with and those without metabolic syndrome. E, peak early diastolic transmitral flow; A, peak late diastolic transmitral flow; E/A , the ratio of E to A; DcT, deceleration time of early diastolic transmitral flow.

syndrome correlate independently with the parameters of LV diastolic function.

Although several recent studies have demonstrated impaired LV systolic and diastolic function in patients with metabolic syndrome (19, 20), consensus is still lacking in regard to the cardiac function in patients with this disease. Wong *et al.* have reported that metabolic syndrome is associated with both LV systolic and diastolic dysfunction (19) in subjects with significant risk factors but no cardiovascular disease. In contrast, Grandi *et al.* have reported that only LV diastolic function is reduced in metabolic syndrome, although LV systolic function is normal in clinically hypertensive non-diabetic subjects (20). Our results agree with the concept that metabolic syndrome is associated with LV diastolic dysfunction even in patients without LV systolic dysfunction. There were no differences in the prevalence of hypertension, diabetes mellitus, or dyslipidemia between the metabolic syndrome and non-metabolic syndrome groups in the current study. However, the BMI, SBP and DBP, and triglycerides were significantly higher in the metabolic syndrome patients than in the non-metabolic syndrome patients. A cluster of these cardiovascular risk factors may produce latent cardiac diastolic dysfunction in metabolic syndrome.

Several limitations exist in assessing cardiac diastolic function by LV diastolic inflow patterns obtained from pulsed Doppler echocardiography. For example, patients with severe

Table 2. Correlation Coefficients of Linear Regression Analysis between *E/A*, Tei Index, and Clinical Parameters

	<i>E/A</i>		Tei index	
	<i>r</i>	<i>p</i> value	<i>r</i>	<i>p</i> value
Age (years)	-0.10	NS	-0.11	NS
BMI (kg/m ²)	-0.28	0.001	0.36	<0.001
Systolic BP (mmHg)	-0.33	<0.001	0.29	0.001
Diastolic BP (mmHg)	-0.23	0.007	0.21	0.014
Fasting blood glucose (mg/dl)	-0.17	0.049	0.32	<0.001
Total cholesterol (mg/dl)	0.07	NS	0.02	NS
HDL cholesterol (mg/dl)	0.26	0.002	-0.23	0.007
LDL cholesterol (mg/dl)	0.08	NS	-0.02	NS
Triglyceride (mg/dl)	-0.34	<0.001	0.32	<0.001

E, peak early diastolic transmitral flow; *A*, peak late diastolic transmitral flow; BMI, body mass index; BP, blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein.

Table 3. Multiple Regression Analysis for *E/A* and Related Parameters

Independent variables	β coefficient	<i>t</i> value	<i>p</i> value
Triglyceride	-0.33	-4.25	<0.001
Systolic BP	-0.31	-4.03	<0.001
<i>F</i> ratio=18.04 <i>r</i> ² =0.22 (<i>p</i> <0.001)			

E, peak early diastolic transmitral flow; *A*, peak late diastolic transmitral flow; BP, blood pressure.

LV systolic dysfunction show a pseudonormalization of LV diastolic inflow patterns, and they demonstrate normal values for *E/A* even if their LV diastolic function is impaired (15, 16). However, all the subjects in the current study showed normal LV systolic function (LVEF $\geq$ 55%) and did not appear to show a pseudonormalization of LV diastolic inflow. Thus, the increase in *A* velocity in patients with metabolic syndrome (Fig. 3) is indicative of augmented atrial contraction, which is compensation for impaired LV relaxation in the early phase of LV diastole. Therefore, the increase in *A* velocity and the decrease in *E/A* were indicative of LV diastolic dysfunction in patients with metabolic syndrome in the current study. Furthermore, we assessed the Tei index to confirm the impaired cardiac diastolic function of metabolic syndrome patients, because the Tei index is influenced by both LV diastolic and systolic function (17, 18). Because LV systolic function is generally normal in patients with a normal LVEF (64 $\pm$ 4%), an increased Tei index in patients with metabolic syndrome is considered to be a reflection of the cardiac diastolic dysfunction. In the present study, the *E/A* and Tei index were both correlated with the components of the Japanese criteria of metabolic syndrome (Table 2). However, the multiple regression analysis demonstrated that the degree of correlation with the components was somewhat different between the *E/A* and Tei index (Tables 3, 4). This discrepancy between the two indexes may have been related to the

fact that, while both indexes reflect the latent cardiac diastolic dysfunction in metabolic syndrome, they also have different rationales, with the *E/A* ratio measuring the peak velocities of intracardiac blood flow and the Tei index measuring the time intervals of intracardiac blood flow.

The present study demonstrates that the parameters of cardiac diastolic function independently correlate with the triglycerides, fasting blood glucose, and SBP, but they do not correlate with the total cholesterol level (Tables 3, 4). It has recently been reported that at least 30% of patients with congestive heart failure have preserved systolic function but diastolic dysfunction (21). The data in the present study indicate the validity of considering the components of the Japanese criteria of metabolic syndrome to be risk factors for heart failure.

We cannot determine the precise mechanism by which cardiac diastolic function in patients with metabolic syndrome is impaired even if cardiac systolic function is preserved. LV hypertrophy, which was assessed by the LV mass index, was not significantly different between patients with and those without metabolic syndrome in the present study. Therefore, LV hypertrophy is not likely to be a cause of cardiac diastolic dysfunction in patients with metabolic syndrome. Several studies of patients with type 2 diabetes mellitus have demonstrated an accumulation of myocardial collagen leading to interstitial and perivascular fibrosis, both of which correlate with LV early diastolic dysfunction (22, 23). Type 2 diabetes mellitus is frequently associated with metabolic syndrome. In the present study, 32% of the patients with metabolic syndrome were diagnosed as having type 2 diabetes mellitus (Table 1). A recent study demonstrated that insulin resistance is associated with impaired diastolic function of the LV in subjects with impaired glucose tolerance and patients with type 2 diabetes (24). Another study (25) showed that amelioration of insulin resistance by pioglitazone selectively improves cardiac diastolic function. Therefore, insulin resistance in patients with metabolic syndrome as well as those with type 2 diabetes may play an important role in car-

Table 4. Multiple Regression Analysis for Tei Index and Related Parameters

Independent variables	β coefficient	<i>t</i> value	<i>p</i> value
Fasting blood glucose	0.33	4.33	<0.001
BMI	0.25	3.24	0.002
Triglyceride	0.25	3.18	0.002
F ratio=15.92 r^2 =0.27 (p <0.001)			

BMI, body mass index; BP, blood pressure.

diac diastolic dysfunction.

Another possible cause of the cardiac diastolic dysfunction observed in patients with metabolic syndrome in the present study may be mild hypertension, which has been shown to be associated with metabolic syndrome. In the present study, both SBP and DBP were significantly higher in patients with metabolic syndrome than in those without it (Table 1). The VS was significantly larger than the PW in metabolic syndrome patients (p <0.001), but this finding was not observed in non-metabolic syndrome patients (Table 1). This increase in VS was consistent with the echocardiographic features previously reported in patients with hypertension (26, 27). In addition, some previous studies have reported that mildly hypertensive patients demonstrated LV diastolic dysfunction without LV hypertrophy (28, 29). Therefore, the mild hypertension seen in some of our patients with metabolic syndrome may have been responsible for the diastolic dysfunction observed in the present study.

In conclusion, patients with metabolic syndrome can show cardiac diastolic dysfunction even if they have neither LV hypertrophy nor systolic dysfunction. In addition, the parameters of cardiac diastolic function independently correlate with triglycerides, fasting blood glucose, and SBP, which are components of the Japanese criteria of metabolic syndrome. Because the preclinical cardiac diastolic dysfunction in patients with metabolic syndrome may lead to heart failure with preserved cardiac systolic function, metabolic syndrome itself may be a cardiac disease equivalent warranting aggressive treatment.

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