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Original article

Is left ventricular diastolic dysfunction independent from presence of hypertension in metabolic syndrome? An echocardiographic study☆

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ABSTRACT

Background: It has been shown that left ventricular diastolic dysfunction (LVDD) develops in patients with metabolic syndrome (MetS). However, there is not sufficient evidence in the literature to determine whether this condition is due to increase in blood pressure, which is frequently encountered in MetS. The purpose of this study was to test the hypothesis whether LVDD in MetS is independent from the presence of hypertension.

Methods: A total of 60 patients diagnosed with MetS and 30 healthy people, who were age- and gender-matched with the patient group, were included in the study as the control group. In the study group, 30 of the patients were normotensive whereas the other 30 had hypertension. Conventional echocardiographic examinations and tissue Doppler imaging were performed besides measurements of demographic and biochemical parameters.

Results: In the hypertensive MetS group, early diastolic filling flow (E), early diastolic mitral annular velocity (E'), and E/A ratio were significantly lower compared to the control group. Late diastolic filling flow (A), deceleration time (DT), late diastolic mitral annular velocity (A'), and E/E' ratio were higher in the hypertensive MetS group than the control group. In the normotensive MetS group, E, E', and E/A ratio were also lower compared to the control group whereas DT, A', and E/E' ratio were higher.

Conclusion: These findings support the idea that LVDD may develop in patients with MetS even in the absence of hypertension. In addition, co-existence of hypertension with MetS contributes to further worsening of diastolic functions.

Introduction

Left ventricular (LV) diastolic dysfunction generally precedes several cardiac signs and symptoms; but can be detected by echocardiographic examination [1,2]. It is demonstrated that even when the patient has normal LV systolic function, diastolic dysfunction is associated with increased mortality and morbidity [3,4]. Diagnosis of subclinical LV dysfunction enables early treatment in order to prevent cardiovascular disease and heart failure [5].

In terms of cardiovascular risks, metabolic syndrome (MetS) is an important problem, showing a steady increase in frequency parallel to the increase in obesity all over the world. It affects more than 30% of the adult population in the USA [6]. MetS can cause many cardiovascular events, including heart failure [7,8]. On the other hand, hypertension is both an important component of MetS and a risk factor for cardiovascular disease [9,10]. It is well known that LV diastolic dysfunction (LVDD) develops in patients with MetS [11–13]. However, there are no sufficient data in the literature to determine whether this condition develops due to hypertension, which usually accompanies MetS; and a consensus on this topic has not been achieved yet [11]. The purpose of this study was to shed light on this issue and test the hypothesis whether LVDD in MetS was independent from the presence of hypertension.

Investigating the diastolic functions of the left ventricle in normotensive and hypertensive individuals diagnosed with MetS and making a comparison of results between these two groups and with

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the results obtained from control subjects were the aims of this study. It is thought that the results obtained from this study can guide close follow-up of patients with MetS for cardiovascular risks.

Materials and methods

Our study population consisted of patients who were referred to our outpatient clinic with the diagnosis of MetS. A total of 148 patients were enrolled in this study. After inclusion and exclusion criteria were applied, 60 patients were available for study.

Overall 60 patients with newly diagnosed MetS were included in the study, 30 normotensive and 30 hypertensive. The patients included were not on any medication. The control group consisted of 30 healthy volunteers who were age- and gender-matched with the study group. Any patients with a previous diagnosis of diabetes mellitus or a fasting plasma glucose ≥110 mg/dL or hemoglobin A1c ≥6.0% were excluded. No patients in the study group had symptoms or signs suggesting coronary artery disease and they had no ischemia on stress electrocardiographic testing or myocardial perfusion scintigraphy. Criteria for exclusion from the study included presence of coronary artery disease, moderate or severe valvular heart disease detected by echocardiography, hypertrophic/dilated/constrictive cardiomyopathy, LV ejection fraction less than 50%, pericardial effusion, non-sinusoidal rhythm (atrial fibrillation, multifocal atrial tachycardia, atrioventricular block, etc.), morbid obesity [body mass index (BMI) > 35 kg/m^2], renal failure (creatinine level >1.4 mg/dL), smoking, alcohol abuse, and familial dyslipidemia.

Our study was approved by the local Ethical Committee and informed consent was obtained from all the participants in the study. Measurements and tests below were applied to the patients in the study group and control group.

Age, height, and waist circumference measurements were entered on the basis of the standardized protocol. Waist circumference was measured at the narrowest level while the abdomen was relaxed. BMI was calculated by dividing the body weight in kilograms by the square of height in meters.

The diagnosis of MetS was established on the basis of the International Diabetes Federation (IDF), Europids criteria [14]. For the diagnosis of MetS, besides abdominal obesity, the presence of at least two of the following criteria has to be met. Abdominal obesity was defined as waist circumference >94 cm for men and >80 cm for women [14].

I. High levels of triglyceride (150 mg/dL).
II. Low levels of high-density lipoprotein (HDL) cholesterol (<40 mg/dL in men, <50 mg/dL in women).
III. High blood pressure (BP) (systolic ≥130 mmHg or diastolic ≥85 mmHg or treatment of previously diagnosed hypertension).
IV. Increased fasting blood glucose level (≥100 mg/dL).

A detailed history was taken and physical examinations were done for each patient. BP was measured at least three times on three different occasions and subsequently confirmed on at least two more visits during the following 2 weeks. BP measurements were carried out from the right arm of the patient in the supine position after at least 5 min of resting in the office. Averages of all measurements were recorded as the BP. For biochemical studies, 12 h of fasting was requested prior to blood sampling. Complete enzymatic technique was utilized for triglyceride level measurement. HDL-cholesterol levels were evaluated following the precipitation process of lipoproteins containing apolipoprotein B using chloride-free dextran sulphate. Plasma glucose levels were measured by glucose oxidase technique using Hitachi brand modular P800i autoanalyzer (Hitachi, Tokyo, Japan).

The echocardiograms were obtained on a Vivid 3 echocardiography device (General Electric-Vingmed, Chalfont St Giles, UK) with a transducer with 2.5 MHz phase. Echocardiography was applied to all groups by the same examiner. Measurements were taken from the long axis parasternal window and apical window, 4 and 5 chamber images with the patient being in the left lateral decubitus position. All measurements were obtained during expirium and simultaneously with electrocardiographic recording of 25 cm/s, calculating the average value of three consecutive measurements.

In Apical 4 chamber imaging, transmitral flow sample was recorded by placing the pulsed wave Doppler (Pw) sample volume on the tips of leaflets of the mitral valve. Peak early diastolic flow velocity (E) and peak late diastolic flow velocity (A) were measured. E-Wave deceleration time (DT) and E/A wave ratios were calculated. Mitral annulus lateral wall E' and A' values were calculated using tissue Doppler. The following cardiac parameters were measured using M mode of 2-D derived image of the heart: posterior wall thickness (PWT) in diastole, interventricular septum thickness (IVST) in diastole and LV end diastolic diameter (LVEDD). LV mass index (LVMI), relative wall thickness (RWT), and left atrial volume index (LAVI) measurements were also made, because of the close relationship with LV or left atrial structure and LV filling [15–17]. LV mass was calculated using the Devereux formula: LVM (g) = $0.8 \times 1.04 \times [(\text{LVEDD} + \text{IVST} + \text{PWT})^3 - \text{LVEDD}^3] + 0.6$. LVMI was calculated by dividing LVM by body surface area. RWT was calculated as (2 × posterior wall thickness)/LV diastolic diameter [17].

Left atrial volume (LAV) was calculated at end-systolic phase using the following formula: $\text{LAV} = (\text{A1} \times \text{A2}) \times 0.85/L$. A1 was defined as the left atrial area using apical ventricular four-chamber in end-systolic phase. A2 was defined as the left atrial area using apical two-chamber in end-systolic phase. L was defined as the long-axis length of the left atrium in the apical four-chamber view [17,18]. Left atrial volume index was calculated by dividing LAV by the body surface area.

In terms of diastolic echocardiographic parameters, the presence of any significant difference between normotensive and hypertensive MetS groups and control group was investigated. Statistical analysis of the results was done using the Statistical Package for the Social Sciences (version 15.0; SPSS Inc., Chicago, IL, USA) for Windows program. Average, standard deviation, and minimum and maximum values were calculated with regard to numeric variables. Continuous variables were tested for normal distribution with the Kolmogorov–Smirnov test. For group comparisons, one-way ANOVA test was used and the Scheffe correction was applied for post hoc analyses. Statistical significance was considered as $p < 0.05$. The relationship between E/E' as a diastolic dysfunction parameter and the variables was evaluated by linear regression analysis and multivariable analysis.

Results

A total of 148 patients were enrolled in this study. Eighty-eight patients were excluded for the following reasons: previous diagnosis of diabetes mellitus or a fasting plasma glucose ≥110 mg/dL or hemoglobin A1c ≥6.0% (37 patients), morbid obesity (32 patients), history of coronary artery disease (5 patients), myocardial ischemia detected by exercise electrocardiogram test or myocardial perfusion scintigraphy (11 patients), history of dilated cardiomyopathy (1 patient), moderate or severe valvular heart disease detected by echocardiography (1 patient had severe mitral stenosis, 1 patient had moderate mitral regurgitation).

After inclusion and exclusion criteria were applied, 90 individuals were included in the study, 30 of whom were hypertensive (HT) with MetS, 30 were normotensive (NT) with MetS, and 30 were healthy volunteers. The age range for the entire study group was 29–61 years and the average age was 44.3 ± 7 years. There was not any difference in terms of demographic variables among the three groups. When the two groups with MetS were compared, systolic and diastolic BPs were higher in the HT MetS group as expected. Other than that, no statistically significant difference was found between the two groups considering other parameters. Evaluation of the groups in terms of the MetS parameters is depicted in Table 1. There was not any difference in regard to fasting blood glucose, triglyceride, and HDL levels between MetS groups (p values were 0.8, 0.2, and 0.1, respectively). No statistically significant difference was observed in terms of body weight, waist circumference, and BMI between the two MetS groups (p values were 1, 1, and 0.6, respectively). Echocardiographically, the LV systolic functions were normal in all individuals and there was not any difference among the groups in terms of ejection fraction (EF). LV IVST, LV PWT, LVMI, RWT, and LAVI were found to be higher in the HT MetS group compared to the other two groups ($p < 0.001$). The LVMI, RWT, and LAVI were not significantly different between the NT MetS group and the control group (p values: 0.9, 0.06, and 0.1, respectively).

In the HT MetS group, the E, the E', and E/A ratio were found to be lower than in the control group (p values <0.001), while the A, DT, A', and E/E' ratio were higher (p values 0.04, 0.001, <0.001, and 0.008 respectively). In the NT MetS group, E, E', and E/A ratio were also lower than in the control group (p values <0.001), whereas DT ($p < 0.001$), A' ($p = 0.03$), and E/E' ratio ($p = 0.003$) were found to be higher. There was no statistically significant difference between NT MetS group and the control group for A. When the HT MetS group was compared to NT MetS group, E and E' were lower, whereas A' and E/E' ratio were higher (p values 0.02, <0.001, 0.04, and 0.02, respectively). No significant differences were detected with regard to other diastolic parameters between the HT and NT MetS groups. The results of echocardiographic parameters and comparison of all three groups are summarized in Table 2. The association between E/E' as a diastolic dysfunction parameter and the variables is presented in Table 3. In linear regression analysis, only the systolic blood pressure was significantly associated with diastolic dysfunction in patients with MetS. The relationship between systolic BP and E/E' ratio is shown in Fig. 1. In multivariate regression analysis excluding BMI and waist circumference, we observed similar findings, indicating that systolic BP was the most significant determinant of E/E' ($p = 0.01$).

Discussion

According to the results of our study, it was shown that LVDD developed regardless of hypertension in our patients with MetS. Comparing the control group to the NT MetS group, many parameters of diastolic function were found to be impaired. In the presence of HT, further impairment was detected in these parameters, suggesting worsening of diastolic function. Even if hypertension does not co-exist with MetS, it was observed that the E, E' values, and E/A ratio decrease while the DT, A' values, and E/E' ratio increase.

Table 1
Clinical characteristics and metabolic syndrome parameters of the study population.

	HT MetS ($n = 30$)	NT MetS ($n = 30$)	Control ($n = 30$)	p
Age (years)	44.8 ± 7.3	45.8 ± 8.1	42.4 ± 5	0.2
Sex, female	10 (33%)	12 (40%)	11 (37%)	NS
Weight (kg)	79.7 ± 10[a]	82.7 ± 8[a]	66 ± 10[b]	<0.001
Height (m)	1.62 ± 3	1.67 ± 2	1.65 ± 2	0.1
BMI (kg/m^2)	30.0 ± 2.2[a]	29.6 ± 2.5[a]	24.1 ± 2.3[b]	<0.001
Waist circumference (cm)	105.2 ± 9.6[a]	105.4 ± 8.2[a]	85.5 ± 7[b]	<0.001
Fasting glucose (mg/dL)	92.0 ± 8.1	91.7 ± 8	93 ± 7	0.8
Systolic BP (mmHg)	149 ± 10[a,b]	114 ± 7	113 ± 9[b]	<0.001
Diastolic BP (mmHg)	88 ± 7.5[a,b]	78.4 ± 7.5	74 ± 6[b]	<0.001
Triglycerides (mg/dL)	201.4 ± 81[a]	244.8 ± 121[a]	102.7 ± 32[b]	<0.001
HDL (mg/dL)	46.2 ± 9.8[a]	41.2 ± 9.4[a]	55.5 ± 9.2[b]	<0.001

HT, hypertensive; NT, normotensive; MetS, metabolic syndrome; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; NS, not significant.
p-Values for one-way ANOVA test.
[a] Statistically significant when compared to the control group in post hoc Scheffe test $p < 0.05$.
[b] Statistically significant when compared to the NT MetS group in post hoc Scheffe test $p < 0.05$.

Table 2
Echocardiographic parameters of LV structure and diastolic function.

	HT MetS ($n = 30$)	NT MetS ($n = 30$)	Control ($n = 30$)	p-Value
E (cm/s)	65 ± 15[a,b]	75 ± 12[a]	89 ± 7[b]	<0.001
A (cm/s)	71 ± 1[a]	69 ± 10	64 ± 10	0.04
DT (ms)	241.3 ± 50[a]	254 ± 53[a]	199.6 ± 15.4[b]	<0.001
E' (cm/s)	7.3 ± 0.4[a,b]	9.8 ± 1.3[a]	14 ± 3[b]	<0.001
A' (cm/s)	11.6 ± 1.0[a,b]	10.6 ± 1.0[a]	9.7 ± 1.9[b]	<0.001
E/E' ratio	8.9 ± 2.2[a,b]	7.7 ± 1.4[a]	6.6 ± 1.3[b]	<0.001
E/A ratio	0.9 ± 0.3[a]	1.1 ± 0.2[a]	1.4 ± 0.1[b]	<0.001
IVST (cm)	1.1 ± 0.1[a,b]	0.9 ± 0.1	0.9 ± 0.07	<0.001
PWT (cm)	1.1 ± 0.08[a,b]	0.9 ± 0.07	0.9 ± 0.07	<0.001
LVMI (g/m^2)	129 ± 22[a,b]	92.1 ± 14	90 ± 12	<0.001
RWT	0.48 ± 0.09[a,b]	0.42 ± 0.08	0.40 ± 0.06	<0.001
LAV index (mL/m^2)	31.5 ± 9[a,b]	24.2 ± 6	23.1 ± 9.4	<0.001

HT, hypertensive; NT, normotensive; MetS, metabolic syndrome; E, early diastolic mitral inflow velocity; A, late diastolic mitral inflow velocity; DT, E-wave deceleration time; E', tissue Doppler early diastolic velocity; A', tissue Doppler late diastolic velocity; IVST, interventricular septum thickness; PWT, posterior wall thickness; LVMI, left ventricular mass index; RWT, relative wall thickness; LAV, left atrial volume.
p-Values for one-way ANOVA test.
[a] Statistically significant when compared to the control group in post hoc Scheffe test $p < 0.05$.
[b] Statistically significant when compared to the NT MetS group in post hoc Scheffe test $p < 0.05$.

Table 3
Linear regression analysis: the association between E/E' as a diastolic dysfunction parameter and the variables in patients with metabolic syndrome.

Variables	Standardized coefficient β (S.E.)	p-Value
Age (years)	−0.28 (0.02)	0.06
Systolic BP (mmHg)	0.32 (0.02)	0.04
Diastolic BP (mmHg)	0.26 (0.03)	0.07
BMI (kg/m^2)	0.18 (0.07)	0.27
Waist circumference (cm)	−0.09 (0.03)	0.55
Fasting glucose (mg/dL)	0.12 (0.01)	0.32
HDL (mg/dL)	0.03 (0.03)	0.8
Triglycerides (mg/dL)	−0.01 (0.002)	0.9

E, early diastolic filling flow; E', early diastolic mitral annular velocity; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein.
Regression coefficient β represents slope estimate ± standard error of the estimate (S.E.).

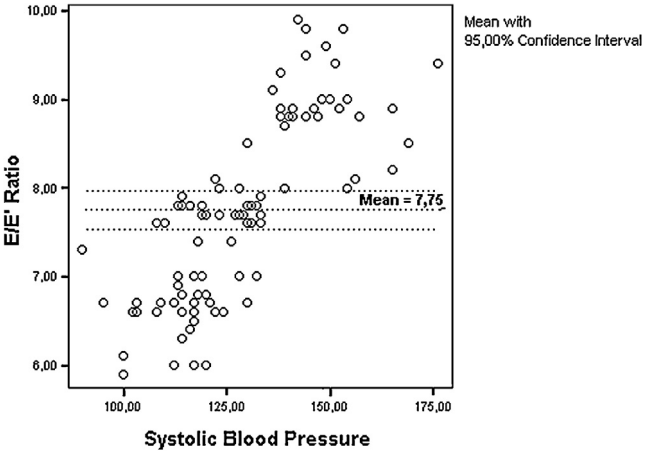

Fig. 1. The relationship between systolic blood pressure and E/E' ratio as a diastolic parameter. E, early diastolic filling flow; E', early diastolic mitral annular velocity.

Change in these parameters refers to an increase in the LV end diastolic pressure [19,20]. For this reason, our findings are important that they indicate for the first time in the literature that an increase in the LV end diastolic pressure, although indirectly, is observed in MetS patients without hypertension.

Since hypertension is also present in most of the patients with MetS, it is hard to determine to what extent hypertension contributes to diastolic impairment. Although there are several studies suggesting that MetS causes deterioration in LV diastolic function [21–23], there is no published article evaluating the exact relationship of MetS with or without hypertension. It is even suggested that hypertension is the primary cause of LVDD in MetS [11]. In previous studies, it has been found that hypertension and obesity are two independent predictors in the development of LVDD in MetS [24–26]. Similar to our results, Masugata et al. showed that LVDD developed independently from LV hypertrophy in MetS and systolic BP, BMI, and triglyceride levels constitute independent risk factors in the development of LVDD [12]. We found that there was no structural remodeling in the NT MetS group by echocardiography. In our study, LVMI, RWT, and LAVI were not significantly different between the NT MetS group and the control group. Therefore, LV hypertrophy is not likely to be a cause of cardiac diastolic dysfunction in patients with MetS. 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 early LVDD [19,21]. Consistent with our results in a study conducted in 1599 subjects MetS and insulin resistance were found to be associated with abnormal LV diastolic function independent of BP and fasting plasma glucose level. However, all patients in this study had hypertension and as expected LV hypertrophy, which was assessed by the LVMI, was significantly different between patients with MetS and those in controls [27]. Gong et al. proved that systolic BP, waist-to-hip ratio, and HDL levels were independent variables in the development of LVDD [11]. Similarly, de las Fuentes et al. examined 607 patients with MetS who had normal LV systolic function and showed that hypertension and obesity constituted independent predictors in the development of LVDD [28]. In all of these studies, it is stated that there is still debate on whether obesity or hypertension causes LVDD and this issue remains to be elucidated [28]. In a study conducted by Seo et al., diastolic function parameters in 42 MetS patients without hypertension were examined by echocardiographic methods and compared to the control group ($n = 20$), a decrease in myocardial systolic and early diastolic flow velocities was observed [29]. However, in this study, the patient group was compared to a control group of only 20 individuals, but no comparison was done with the hypertensive MetS group. Besides, this study was conducted on a different ethnic group (Asian population). It is known that cardiac structure and functions vary among ethnic groups [30,31]. For this reason, different diagnostic criteria were used in different ethnic groups in IDF diagnostic criteria for the MetS [14].

We observed a linear association with systolic BP and E/E' in linear regression analysis. Increased afterload or end-systolic BP primarily prolongs the rate of LV relaxation [32]. Therefore, systolic BP is an important determinant of diastolic function even within the normal range. MetS can augment effects of systolic BP on relaxation; hence even normal range systolic BP can impair LV relaxation in subjects with MetS. Our findings support the notion that a lower BP target should be selected for patients with MetS. Therefore, the presence of MetS in these patients may impair diastolic relaxation by disturbing end-systolic BP and LV end-systolic volume relationship.

Prior studies have demonstrated that patients with diastolic dysfunction and normal systolic function have an increase in all-cause mortality, independent of age, sex, and EF. The development of diastolic dysfunction without coexisting hypertension is an important finding and may be responsible for some part of high cardiovascular mortality and morbidity in patients with MetS.

Findings in our study have shown that even when hypertension does not co-exist with MetS, subclinical LVDD can develop. However, MetS is a complex syndrome because it consists of many variables (hypertension, obesity, diabetes mellitus, hyperlipidemia, etc.) that affect cardiac structure and functions. One of the components of MetS is insulin resistance. But it is not required to establish MetS diagnosis [14,33]. We could not measure serum insulin resistance of patients in our study. Since obesity itself causes LVDD, morbid obese patients (those with BMI >35) were not included in our study, however, as expected, BMI was above normal values in our study group. The size of our study population was small due to low prevalence of normotensive MetS and the patients were derived from a single center. Although we did not show a correlation between BMI and E/E', many studies have demonstrated a link between BMI and LVDD [34]. It may be related to the small size of our study population. But a larger number of MetS patients should be evaluated in this regard.

Conclusion

Patients with MetS display diastolic dysfunction even in the absence of high BP or LV hypertrophy. The mechanism may be related to augmentation of BP effects on LV relaxation in subjects with MetS. Therefore diastolic dysfunction can be observed in the

presence of normal or low BP in patients with MetS. Diagnosis of subclinical LV dysfunction enables early treatment in order to prevent cardiovascular disease and heart failure.

Conflict of interest

There is no conflict of interest between the authors.

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