

Impaired right ventricular functions in metabolic syndrome patients with preserved left ventricular ejection fraction

Sol ventrikül ejeksiyon fraksiyonu korunmuş olan metabolik sendromlu hastalarda bozulmuş sağ ventrikül fonksiyonları

Özlem Karakurt, M.D., Sanem Öztekin,[#] M.D., Nuray Yazıhan, M.D.,[†] Ramazan Akdemir, M.D.

Departments of Cardiology and [#]Internal Medicine, Dışkapı Yıldırım Beyazıt Training and Research Hospital;

[†]Molecular Biology Research and Development Unit, Medicine Faculty of Ankara University, both in Ankara

ABSTRACT

Objectives: Metabolic syndrome (MetS) has been shown to be independently associated with increased risk for incident heart failure and coronary artery disease. We investigated whether there was deterioration in right ventricular functions in MetS patients with preserved left ventricular functions and its association with the number of MetS components.

Study design: The study included 192 consecutive patients (148 women, 44 men; mean age 54.3±8.5 years) with the diagnosis of MetS based on the NCEP-ATP III criteria and 20 healthy controls (12 women, 8 men; mean age 51.6±8.4 years). All subjects underwent conventional and tissue Doppler (TDI) echocardiography to assess left and right ventricular functions, including right ventricular myocardial performance index (MPI) and tricuspid annular plane systolic excursion (TAPSE).

Results: The number of MetS components were three in 43.8%, four in 31.3%, and five in 25% of the patients. Right ventricular TDI-derived MPI was higher in patients with MetS compared to controls [median 0.5 (range 0.2-3.3) vs. 0.3 (0.1-0.7), p=0.000]. This was possibly due to significantly shortened right ventricular ejection time in MetS patients (p<0.05). Although TAPSE was within the normal range in MetS patients, it was significantly decreased compared to controls (p=0.000), accompanied by significantly lower TDI-derived S wave, E wave, and E/A ratio (p=0.000). None of the MetS components were significantly correlated with right ventricular TDI-derived MPI. There was no association between the number of MetS components and echocardiographic parameters.

Conclusion: Our findings show that, despite preserved left ventricular systolic functions, both systolic and diastolic functions of the right ventricle deteriorate in MetS patients.

ÖZET

Amaç: Metabolik sendromun (MetS) kalp yetersizliği ve koroner arter hastalığının bağımsız risk faktörlerinden biri olduğu ortaya konmuştur. Bu çalışmada, sol ventrikül fonksiyonları korunmuş MetS hastalarında sağ ventrikül fonksiyonlarında bozulma olup olmadığı ve bu durumun MetS bileşeni sayısı ile ilişkisi araştırıldı.

Çalışma planı: Çalışmaya NCEP-ATP III ölçütlerine göre MetS tanısı konan 192 hasta (148 kadın, 44 erkek; ort. yaş 54.3±8.5) ve kontrol grubu olarak 20 sağlıklı gönüllü (12 kadın, 8 erkek; ort. yaş 51.6±8.4) alındı. Tüm olgulara konvansiyonel ve doku Doppler ekokardiyografi yapılarak sol ve sağ ventrikül fonksiyonları incelendi ve sağ ventrikül miyokart performans indeksi (MPI) ve triküspit halka düzleminde sistolik yer değiştirme (TAPSE) hesaplandı.

Bulgular: Hastaların %43.8'inde üç, %31.3'ünde dört, %25'inde beş adet MetS bileşeni vardı. Kontrol grubu ile karşılaştırıldığında, sağ ventrikül doku Doppler MPI MetS grubunda daha yüksek bulundu [ortanca 0.5 (dağılım 0.2-3.3) ve 0.3 (0.1-0.7), p=0.000]. Bu durumun MetS hastalarında sağ ventrikül doku Doppler ejeksiyon zamanındaki anlamlı azalmadan kaynaklandığı düşünüldü (p<0.05). Hasta grubunda TAPSE normal sınırlarda bulunmasına karşın, kontrol grubundan anlamlı derecede düşük idi (p=0.000); ayrıca, doku Doppler ile ölçülen S dalgası, E dalgası ve E/A oranı da anlamlı derecede düşük bulundu (p=0.000). Metabolik sendrom bileşenlerinin hiçbiri sağ ventrikül doku Doppler MPI ile anlamlı ilişki göstermedi; MetS bileşenlerinin sayısı da ekokardiyografik bulgularla ilişkili değildi.

Sonuç: Bulgularımız, sol ventrikül fonksiyonları henüz korunmuş olsa da, MetS hastalarında sağ ventrikülün sistolik ve diyastolik fonksiyonlarında bozulma meydana geldiğini göstermektedir.

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Correspondence: Dr. Özlem Karakurt, Balıkesir Devlet Hastanesi, Kardiyoloji Kliniği, 10000 Balıkesir, Turkey.
Tel: +90 266 - 245 90 20 e-mail: ozlemkarakurt55@yahoo.com

Metabolic syndrome, also called insulin resistance syndrome, consists of a clustering of several metabolic and physiological risk factors, including obesity and its central distribution, impaired glucose regulation, dyslipidemia (elevated triglycerides and/or low HDL cholesterol), and hypertension. It has received great attention after being understood that it carries increased risk for development of type 2 diabetes mellitus and atherosclerotic cardiovascular disease. Studies have demonstrated that MetS is also associated with left ventricular hypertrophy, LV diastolic and myocardial dysfunction.^[1] Voulgari et al.^[2] found that MetS patients have higher LV myocardial performance index, i.e., Tei index, values compared to normal subjects, indicating depressed ventricular functions. Another recent study demonstrated that MetS predicted congestive heart failure independent of interim myocardial infarction and prevalent diabetes in elderly Finns during a follow-up of 20 years.^[3]

The Tei Index (a combined MPI) has become a valuable echocardiographic index for the assessment of global systolic and diastolic function.^[4]

An increased Tei index is a strong predictor of mortality and morbidity in patients with dilated cardiomyopathy, cardiac amyloidosis, acute myocardial infarction, congenital heart disease, and primary pulmonary hypertension.^[5-12] Many studies have shown that the Tei index is also a powerful indicator of right ventricular functions. Pulsed-wave Doppler-derived Tei index has been shown to provide reliable information on detecting RV functions.^[9,13] Tissue Doppler-derived Tei index has also been found to correlate well with pulsed-wave Doppler measurements.^[14,15] Even in fetuses, RV TDI-derived Tei index correlated well with pulsed-wave Doppler.^[16] Chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, congenital heart disease, pulmonary hypertension, obstructive sleep apnea syndrome, and pulmonary embolism are some of the diseases that have been shown to be associated with increased MPI of the RV.^[17-19] Right ventricular MPI is not only a powerful diagnostic tool, but also a valuable index for predicting prognosis.

Abbreviations:

<i>Aa</i>	Late diastolic velocity
<i>Ea</i>	Early diastolic velocity
<i>ET</i>	Ejection time
<i>IVCT</i>	Isovolumetric contraction time
<i>IVRT</i>	Isovolumetric relaxation time
<i>LV</i>	Left ventricle
<i>MPI</i>	Myocardial performance index
<i>MetS</i>	Metabolic syndrome
<i>RV</i>	Right ventricle
<i>Sa</i>	Systolic velocity
<i>TAPSE</i>	Tricuspid annular plane systolic excursion
<i>TDI</i>	Tissue Doppler imaging

Although there are many studies demonstrating decreased LV diastolic functions in MetS, there is only one study investigating RV functions in this patient group.^[20] Tadic et al.^[20] demonstrated that RV global functions were impaired in MetS patients and this impairment was related to MetS components.

In this study, we investigated whether there was deterioration in RV functions in MetS patients with preserved LV functions and the association of this impairment with the number of MetS components.

PATIENTS AND METHODS

The study included 192 consecutive patients (148 women, 44 men; mean age 54.3±8.5 years) with MetS. A control group of 20 healthy volunteers (12 women, 8 men; mean age 51.6±8.4 years) were enrolled into the study for comparison. Healthy volunteers were chosen from those who presented to the internal medicine outpatient clinic with varying complaints, but were found to be disease free. The diagnosis of MetS was based on the NCEP-ATP III guidelines as presence of at least three of the five following criteria: abdominal obesity (waist circumference >102 cm in men, >88 cm in women); hypertriglyceridemia (>150 mg/dl); low HDL cholesterol level (<40 mg/dl in men, <50 mg/dl in women); high blood pressure (>130/85 mmHg); and high fasting glucose (>110 mg/dl).^[21] Exclusion criteria were defined as the presence of any of the following: atrial fibrillation or flutter, bundle branch block or any other intraventricular conduction delay; recent major surgical procedure in the past month; acute coronary syndromes; malignancies; pulmonary emboli; chronic obstructive pulmonary disease, asthma, or other pulmonary diseases; renal failure; history of previous myocardial infarction or coronary artery bypass graft operation, stroke, heart failure, or angina; congenital, pericardial, or severe valvular heart disease; LV ejection fraction <55%; LV wall motion abnormality; pregnancy; thyroid disorders; and inflammatory diseases such as infections and autoimmune disorders.

The study was approved by the institutional ethics committee and written informed consent was obtained from all participants before the study.

Blood sampling protocol

Peripheral venous blood samples were obtained following an overnight fasting period. Blood glucose, lipid parameters, liver function tests, HbA_{1c} were

measured on P800 Roche Hitachi and Olympus AU 5200 automated analyzers. Low-density lipoprotein cholesterol was calculated using the Friedewald formula. Complete blood counts were performed on a Roche Sysmex SE-9000 automated analyzer. Plasma insulin levels were measured using a commercial human insulin ELISA kit (Linco Research, MO, USA) following the protocol suggested by the manufacturer. The HOMA (Homeostatic Model Assessment) index was calculated as the product of the fasting plasma insulin level (microU/ml) and the fasting plasma glucose level (mmol/l), divided by 22.5.

Echocardiographic measurements

All patients underwent conventional echocardiography using a GE Vivid 3 (Isreal) echocardiography device. Echocardiographic measurements were performed according to the recommendations of the American Society of Echocardiography.^[22] Left ventricular volumes and ejection fraction were obtained by the modified biplane Simpson’s method. Left atrial, LV end-diastolic and end-systolic dimensions, inter-ventricular septal thickness, and LV end-diastolic posterior wall thickness were measured from the parasternal long-axis view. From the apical 4-chamber view, mitral inflow E and A velocities were measured and then the TDI cursor was placed on the lateral wall of the LV, 1 cm apical to the mitral annulus. From TDI of the LV lateral annulus, systolic velocity (Sa), early diastolic velocity (Ea), and late diastolic velocity (Aa) were recorded. Left ventricular diastolic functions were graded.

For the assessment of RV functions, the TDI cursor was placed on the RV free wall, 1 cm apical to the tricuspid annulus from the apical 4-chamber view and Sa, Ea, and Aa were recorded. The pulse-wave Doppler velocity range was -20 to 20 cm/sec. On the TDI images, ejection time (Sa duration), isovolumetric relaxation time (time between the end of Sa and the beginning of Ea), and isovolumetric contraction time (time between the end of Aa and the beginning of Sa) were measured. Right ventricular Tei index was calculated as shown in Fig 1. Mean pulmonary artery pressure was calculated using the Mahan method from RV acceleration time.^[23] Tricuspid annular plane systolic excursion was measured by two-dimensional echocardiography-guided M-mode recordings from the apical 4-chamber view with the cursor placed at the free wall of the tricuspid annulus as previously described.^[24] Care was taken to align the sample volume as vertical as possible with respect to the cardiac apex. Angle correction and re-

spiratory gating were not used. Maximal TAPSE was determined by the total excursion of the tricuspid annulus from its highest position after atrial ascent to the lowest point of descent during ventricular systole. Left ventricular mass index was calculated using the Devereux’s formula.^[25] Left ventricular hypertrophy was defined as LV mass index >134 g/m² in men and >110 g/m² in women.

Statistical analysis

Data were analyzed with the SPSS version 15.0 for Windows software package. Continuous variables were presented as mean±SD and categorical variables as frequency and percentage. The Student’s t-test was used to compare normally distributed continuous variables and the Mann-Whitney U-test was used for variables without normal distribution. Categorical variables were compared using the chi-square test. Correlations were sought using the Spearman and Pearson correlation analyses where appropriate. A value of less than 0.05 was considered significant.

RESULTS

Demographic, clinical, and echocardiographic variables of the two groups are summarized in Table 1. The most frequent MetS criterion was increased waist circumference, which was above the upper limits in 156 patients (81.3%). Among MetS patients, only 10

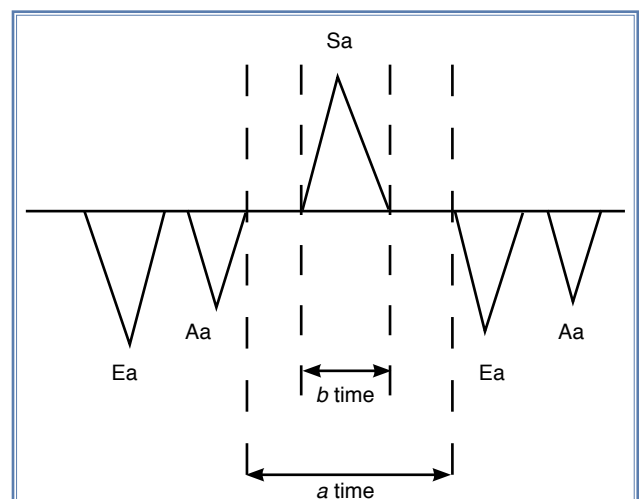


Figure 1. Estimation of right ventricular Tei index (myocardial performance index) by tissue Doppler imaging. Tei index= [(a-b)/b], where a denotes the sum of isovolumetric relaxation time, isovolumetric contraction time, and ejection time; b is equal to ejection time. Sa: Systolic velocity; Ea: Early diastolic velocity; Aa: Late diastolic velocity.

Table 1. Demographic and clinical characteristics and echocardiographic findings of the subjects with and without metabolic syndrome

	Metabolic syndrome (n=192)			Controls (n=20)			p
	n	%	Mean±SD/ Median (range)	n	%	Mean±SD/ Median (range)	
Age (years)			54.3±8.5			51.6±8.4	0.10
Sex							0.10
Female	148	77.1		12	60.0		
Male	44	22.9		8	40.0		
Body mass index (kg/m ²)			31.6 (22.9-49.1)			23 (19-27)	0.000
Waist circumference (cm)			103.5±9.8			84.7±6.8	0.000
Smoking	37	19.3		5	25.0		0.20
Hypertension	152	79.2		–			0.000
Fasting plasma glucose (mg/dl)			117.5 (64-380)			90.5 (67-110)	0.000
HDL cholesterol (mg/dl)			44.6±12.2			51.8±9.1	0.006
Triglyceride (mg/dl)			180 (40-1729)			133 (97-167)	0.000
Systolic blood pressure (mmHg)			132.1±19.6			112.3±8.0	0.000
Diastolic blood pressure (mmHg)			79.4±11.8			70.9±7.2	0.012
Echocardiographic findings							
Left ventricle							
Ejection fraction (%)			68.4 (58-77)			68.7 (65-70)	0.45
Mitral inflow E wave (m/sec)			0.7 (0.4-1.1)			0.8 (0.7-1.0)	0.000
Mitral inflow A wave (m/sec)			0.8 (0.1-1.3)			0.6 (0.5-0.6)	0.000
Isovolumetric relaxation time (msec)			108.3±23.3			82.6±4.4	0.000
Deceleration time (msec)			215.9±48.5			188.0±14.1	0.000
Lateral annulus E' wave (cm/sec)			8.1 (3.0-19.0)			10.0 (8.9-15.0)	0.000
Lateral annulus A' wave (cm/sec)			11.0 (4.0-20.0)			6.7 (5.9-8.9)	0.000
Myocardial performance index			0.6 (0.2-1.47)			0.3 (0.3-0.4)	0.000
Right ventricle							
Myocardial performance index			0.5 (0.2-3.3)			0.3 (0.1-0.7)	0.000
TAPSE (cm)			2.1 (1.3-3.1)			2.9 (2.1-3.5)	0.000
Tissue Doppler b time (msec)			269 (171-468)			314 (272-374)	0.000
Tissue Doppler a time (msec)			396.4±56.2			395.6±40.0	0.95
S wave (cm/sec)			13.0 (7.0-26.0)			16.0 (13.5-23.0)	0.000
E wave (cm/sec)			9.0 (4.0-20.0)			14.5 (8.0-22.0)	0.000
A wave (cm/sec)			15.5±4.8			17.0±5.4	0.18
E/A			0.7 (0.2-2.0)			0.9 (0.0-1.0)	0.000
Mean pulmonary artery pressure (mmHg)			27.0±10.8			17.5±3.7	0.000

TAPSE: Tricuspid annular plane systolic excursion.

(5.2%) had normal weight, 56 patients (29.2%) were overweight, 117 patients (60.9%) had grade 1 or 2 obesity, and nine patients (4.7%) were morbid obese. Diabetes was present in 111 patients (57.8%) and a high fasting plasma glucose level was detected in 135 patients (70.3%). The HOMA index was <2.5 in 137

patients (71.4%), and >2.5 in 55 patients (28.7%). Low HDL and high triglyceride levels were seen in 78.1% (n=150) and 79.7% (n=153), respectively. The number of MetS components were three in 43.8% (n=84), four in 31.3% (n=60), and 25% of the patients (n=48) had all the components.

Table 2. The results of correlation analysis

	Myocardial performance index					
	Right ventricle (RV)		Left ventricle (LV)		TAPSE	
	r	p	r	p	r	p
Left atrium diameter	-0.14	0.04				
Right atrium diameter					-0.24	0.00
Mitral inflow E wave	-0.21	0.00			0.20	0.00
Mitral inflow A wave					0.17	0.01
LV isovolumetric relaxation time	0.17	0.01	0.17	0.01		
LV ejection fraction	-0.19	0.00	0.14	0.04	0.15	0.04
RV TDI-derived A wave					0.26	0.00
RV TDI-derived E wave	-0.26	0.00			0.33	0.00
RV TDI-derived S wave	-0.15	0.03			0.37	0.00
RV TDI-derived a time	0.32	0.00	0.16	0.02		
RV TDI-derived b time	-0.67	0.00				
TAPSE	-0.25	0.00				
LV myocardial performance index	0.20	0.00				
LV mass index	-0.06	0.35				
Mitral inflow E wave/LV TDI-derived E wave			0.18	0.00		
LV TDI-derived E wave			-0.22	0.00		
LV TDI-derived S wave			-0.20	0.00		
LV TDI-derived a time			0.35	0.00		
LV TDI-derived b time			-0.46	0.00		
RV TDI-derived A wave			-0.18	0.01		
RV myocardial performance index			0.20	0.00	-0.25	0.00
Isovolumetric contraction time					-0.16	0.02
HDL cholesterol					0.14	0.04
Triglycerides					-0.15	0.03

TAPSE: Tricuspid annular plane systolic excursion; TDI: Tissue Doppler imaging.

The mean LV ejection fraction was 68.4% (range 58%-77%) in the MetS group. Diastolic function was normal in 62 patients (32.3%) and abnormal in 130 patients (67.7%) (grade 1 in 64.1% and grade 2 in 3.6%). Diastolic dysfunction was more frequently seen in MetS patients both in mitral inflow and mitral annular examination.

In the comparison of RV function, RV TDI-derived MPI was higher in patients with MetS compared to controls (Table 1), which was possibly due to shortening of RV ejection time (TDI-derived time) in MetS patients, because TDI-derived time was similar in the two groups. Although TAPSE value was within the normal range in MetS patients,

it was relatively decreased compared to normal subjects, accompanied by lower TDI-derived S wave, E wave amplitudes and E/A ratio. The mean pulmonary artery pressure was higher in MetS patients than the control group (27.0 ± 10.8 vs 17.5 ± 3.7 mmHg, $p=0.000$) (Table 1).

The results of correlation analysis are shown in Table 2. Right ventricular TDI-derived MPI was positively correlated with LV IVRT, RV TDI-derived a time, LV TDI-derived MPI, and inversely correlated with LA diameter, mitral inflow E wave, LV EF, RV TDI-derived E and S waves, b time, and TAPSE (Table 2). There was no correlation between RV TDI-derived MPI and LV mass index.

None of the MetS components were significantly correlated with RV TDI-derived MPI. There was no association between the number of MetS components and echocardiographic parameters.

DISCUSSION

Many studies on the effect of MetS on cardiovascular system have demonstrated its detrimental effects for coronary heart disease and heart failure.^[26] In a 20-year follow-up study of 1,032 Finns, in which subjects with interim myocardial infarction during the follow-up and with prevalent diabetes were excluded, MetS was significantly associated with a 1.37-1.87-fold risk for incident heart failure after adjustment for confounding factors.^[31] Metabolic syndrome was found to be associated with LV hypertrophy, increased LV dimension, relative wall thickness, left atrial diameter, lower ejection fraction, mid wall shortening and mitral E/A ratio after controlling for confounders.^[27,28] In another study, it was demonstrated that TDI-derived septal E wave velocity and global E wave velocity were significantly lower in both MetS and pre-MetS subjects compared to controls.^[29] The prevalence of diastolic dysfunction was reported to be 35% in patients with MetS, which accounted for approximately four-fold increased risk compared to normal participants.^[29]

Turhan et al.^[30] demonstrated that not only diastolic functional parameters, but also MPI, an index of global ventricular function, were worsened in patients with MetS compared with control subjects. As the myocardial function deteriorates, ejection time shortens and IVRT and IVCT lengthens, leading to an increased Tei index. Rivas-Gotz et al.^[31] reported that shortened ejection time and lengthened IVCT reflected systolic dysfunction, whereas lengthened IVRT reflected diastolic dysfunction. Our study confirms these findings, where we also observed a significantly decreased Tei index in the MetS group. This significant association with both systolic and diastolic TDI parameters suggests that both systolic and diastolic functions worsen simultaneously in patients with MetS, before it is manifest in global systolic functional parameters like ejection fraction.

Studies have demonstrated that RV TDI-derived Tei index is a simple and valuable method of assessing RV global function.^[32-34] Right ventricular TDI measurements are used to diagnose many diseases and predict prognosis.^[17-19] Among these, TAPSE has received significant attention in the past years as an

easily measured index for RV functions. It has been reported that TAPSE <2 cm denotes RV dysfunction of varying degrees. Miller et al.^[33] demonstrated that a TAPSE value below 1.5 cm predicted RV EF to be less than 50% with 60% sensitivity and 95% specificity. Right ventricular TDI-derived E wave and E/A ratio were found to be valuable indices for evaluating RV diastolic functions.^[35-42] In addition, TDI-derived S wave is a good indicator of global RV systolic function. Miller et al.^[33] showed that a TDI-derived S wave below 10 cm/sec predicted RV EF to be less than 50% with 59% sensitivity, 92% specificity, and 89% negative predictive value.

The first study on RV functions in MetS patients was reported by Tadic et al.,^[20] in which MetS was found to be related to RV dysfunction, caused by RV hypertrophy, increased right atrial volume and RV Tei index. In our study, RV TDI-derived MPI was significantly increased in MetS patients compared to normal subjects. Also TAPSE, RV TDI-derived S and E waves, time, and E/A ratio were lower in MetS patients. One of the main findings of this study is that, although it remained within normal limits, TAPSE was significantly lower in MetS patients compared to controls. This may point out to occult RV dysfunction. Both MPI and TAPSE showed significant correlations with morphological and functional parameters of the left heart.

In contrast to the findings of Tadic et al.,^[20] we did not find significant associations between MetS components and echocardiographic parameters, except for weak correlations between triglycerides, HDL cholesterol and TAPSE.

In the light of these findings, both systolic and diastolic functions of RV deteriorate in MetS patients even though LV systolic functions are still preserved.

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Key words: Echocardiography, Doppler; metabolic syndrome X; myocardial contraction; ventricular function, right.

Anahtar sözcükler: Ekokardiyografi, Doppler; metabolik sendrom X; miyokart kontraksiyonu; ventrikül fonksiyonu, sağ.