Metabolic Syndrome Is Associated with Atrial Electrical and Mechanical Dysfunction

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Abstract

Objective: In this study, we aimed to investigate the left atrial (LA) electrical and mechanical functions in patients with metabolic syndrome (MetS). *Subjects and Methods:* The study population consisted of 87 patients with MetS and 67 controls. Intra-atrial and interatrial electromechanical delays (EDs) were measured with tissue Doppler imaging. P-wave dispersion (Pd) was calculated from the 12-lead electrocardiograms. LA volumes were measured echocardiographically by the biplane area-length method. *Results:* Intra-atrial and interatrial EDs and Pd were significantly higher in patients with MetS (10.3 ± 6.3, 21.0 ± 11.5 and 41.7 ± 10.8) than in controls (7.4 ± 5.5, 12.3 ± 10.4 and 29.2 ± 7.4; p = 0.003, p < 0.001 and p < 0.001, respectively). The LA preatrial contraction volume and active emptying volumes were higher in this population, but the LA passive emptying fraction was lower. In the multivariate linear regression analysis, the presence of MetS, LA active emptying volume and left ventricular early diastolic (E) wave velocity/late diastolic (A) wave velocity (E/A) ratios were independent correlates of interatrial ED (p = 0.002, p = 0.001 and p = 0.025, respectively). *Conclusions:* This study showed that intra-atrial and interatrial EDs and Pd were prolonged and LA mechanical functions were impaired in patients with MetS.

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Introduction

Metabolic syndrome (MetS) is characterized by a cluster of cardiovascular risk factors including hypertension, abdominal obesity, insulin resistance, dyslipidemia and high levels of inflammatory factors [1, 2]. MetS is highly prevalent in the general population and is related to an increased risk of cardiovascular disease [3, 4]. An increased risk of atrial arrhythmias has also been reported in patients with MetS [5, 6]. The prolongation of intra-atrial and interatrial electromechanical delays (EDs) and the inhomogeneous propagation of sinus impulses are well-known electrophysiologic characteristics of atria prone to fibrillation. This issue has been evaluated non-invasively by P-wave dispersion (Pd) and tissue Doppler imaging (TDI) [7, 8]. Recently, left atrial (LA) mechanical functions were evaluated in patients with MetS [9]. In this study, we aimed to investigate LA electrical and mechanical functions in this group of patients.

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Subjects and Methods

Study Population

The study population was recruited from our outpatient clinic between January 2011 and November 2012. Subjects who fulfilled the criteria for MetS according to the results of recent laboratory tests were prospectively evaluated. The population consisted of 87 patients with MetS (54 males and 33 females) and 67 control patients without MetS (40 males and 27 females). Physical examination and transthoracic echocardiography were performed, and 12-lead electrocardiograms (ECGs) were obtained for each subject. Patients with a history of coronary artery disease, left ventricular (LV) wall motion abnormality, an ejection fraction of <50%, valvular heart disease, primary cardiomyopathy, bundle branch block, atrioventricular conduction anomalies on ECG, anemia, electrolyte imbalance, renal failure, pulmonary disease or poor-quality echocardiographic and electrocardiographic images were excluded. Subjects with more than mild valvular regurgitation (assessed qualitatively with color Doppler imaging) and valvular stenosis of any extent were also excluded. Patients who were on medication that could affect ECG, such as antiarrhythmics, tricyclic antidepressants, beta-blockers and nondihydropyridine calcium-channel blockers, were excluded. The initial study population consisted of 98 patients with MetS; 11 patients were then excluded due to the aforementioned exclusion criteria. All patients were in sinus rhythm. MetS was defined according to the International Diabetes Federation criteria, with abdominal obesity (waist circumference >94 cm for males and >80 cm for females) being a feature as well as at least 2 of the following 4 parameters: hypertension (systolic blood pressure >130 mm Hg and/or diastolic blood pressure >85 mm Hg), a history of antihypertensive usage or hypertriglyceridemia (≥150 mg/dl) and treatment for this disorder, a low level of high-density lipoprotein cholesterol (<40 mg/dl in males and <50 mg/dl in females) and treatment for this disorder, a high fasting plasma glucose (>100 mg/dl) or a diagnosis of type 2 diabetes mellitus [10]. Obesity was defined as a BMI of >30. This study was approved by the Dr. Siyami Ersek Hospital Ethics Committee, and all patients gave their written informed consent.

Conventional Echocardiography

In all subjects, 2-dimensional, M-mode, pulsed-wave and color-flow Doppler echocardiographic examinations (iE33, Philips Medical Systems, Bothell, Wash., USA) were performed by 2 cardiologists (H.Y. and B.G.) who were blinded to the clinical details of the patients. All patients were imaged in the left lateral decubitus position. During echocardiography, a 1-lead ECG was recorded. Two-dimensional and conventional Doppler examinations were obtained in the parasternal and apical views according to the guidelines of the American Society of Echocardiography [10–12]. Three consecutive cycles were averaged for every parameter. LV diameter, interventricular septal and posterior wall thickness and LV ejection fraction were measured by M-mode echocardiography. LV mass and LV mass index (LVMI) were measured. To determine LV mass, the Devereux formula was used. LVMI was calculated by dividing LV mass by body surface area and height [11]. Pulsed-wave Doppler was performed to record LV inflow velocities. Doppler echocardiographic measurements were performed according to the American Society of Echocardiography guidelines [12]. The early diastolic (E) wave and late diastolic (A) wave velocities, E/A ratio, isovolumic relaxation time and deceleration time were measured.

Assessment of LA Volumes and Mechanical Functions

LA volumes were measured echocardiographically by the biplane area-length method from the apical 2- and 4-chamber views. LA volumes were determined at three points: (1) just before mitral valve opening, i.e. maximal (Vmax), (2) at the onset of the atrial systole, i.e. at the onset of the P-wave on electrocardiography (pre-atrial contraction volume, Vp) and (3) at the mitral valve closure, i.e. minimal (Vmin). The following LA emptying function parameters were calculated:

LA passive emptying volume = Vmax – Vp, LA passive emptying fraction = LA passive emptying volume/Vmax, LA conduit volume = LV stroke volume – (Vmax – Vmin), LA active emptying volume = Vp – Vmin, LA active emptying fraction = LA active emptying volume/Vp and LA total emptying volume = Vmax – Vmin. All volumes were indexed to body surface area and expressed in ml/m².

Atrial Electromechanical Coupling and Tissue Doppler Echocardiography

TDI was performed with transducer frequencies of 3.5–4.0 MHz by adjusting the spectral pulsed Doppler signal filters until a Nyquist limit of 15–20 cm/s was reached, and by using the minimal optimal gain. The monitor sweep speed was set at 50–100 mm/s. In the apical 4-chamber view, the pulsed-wave Doppler sample volume was placed at the level of the LV lateral and septal mitral annuli. The atrial electromechanical coupling, i.e. the time interval from the onset of the P-wave on the surface ECG to the beginning of the A wave (PA), was obtained from the lateral mitral annulus (PAlateral), septal mitral annulus (PAseptal) and tricuspid annulus (PAtricuspid). These values were corrected for heart rate by dividing with the square root of the R-R interval [13]. The difference between corrected PAlateral and corrected PAtricuspid was defined as the interatrial ED, while the difference between corrected PAseptal and corrected PAtricuspid was defined as the intra-atrial ED [14].

The peak systolic myocardial velocity (Sm) and early and late diastolic myocardial velocities (Em and Am) were obtained at the lateral and septal mitral annuli. The global Sm, Em and Am were derived as an average from these two annular sites. All echocardiographic measurements were obtained by 2 experienced echocardiographers (H.Y. and B.G.). All echo images were analyzed independently and blinded from patients clinical characteristics by using an off-line system.

P-Wave Dispersion Measurements

All subjects underwent a standard 12-lead surface ECGs recorded at a paper speed of 25 mm/s and a gain of 10 mm/mV (Cardiofax GEM; Nihon Kohden Corp., Tokyo, Japan). All patients were in sinus rhythm during the analysis. The ECGs were transferred to a personal computer by scanner and then magnified (×400) with Adobe Photoshop software (Adobe Systems, Mountain View, Calif., USA). The beginning of the P-wave was defined as the point at which the initial deflection of the P-wave crossed the isoelectric line, and the end of the P-wave was defined as the end of the deflection crossing the isoelectric line. Maximum and minimum P-wave durations (Pmax and Pmin) were measured. The difference between the Pmax and the Pmin was defined as the Pd. Mean values for three complexes were calculated in each lead.

Reproducibility

Ten subjects in each group were randomly selected for interobserver and intraobserver variability. To test the intraobserver vari-

ability, the Vmax, Vmin, Vp and PAlateral, PAseptal and PAtricuspid were remeasured by the same observer from the digital data using an off-line system. Interobserver variability was determined by having a second observer measure these variables from the digital data using an off-line system.

Statistical Analysis

Statistical analyses were performed using SPSS v15.0 for Windows. For evaluation of the data obtained from the study, descriptive statistical methods of mean ± standard deviation, frequency and ratio values were used (see tables 1–3). Categorical data were compared with the χ^2 test. Mean values of continuous variables were compared between groups using the Student t test or the Mann-Whitney U test. The relationship between parameters was determined using Pearson's coefficient of correlation. The independent correlates of atrial conduction times were assessed using multivariate linear regression analysis. The effect of clinical and echocardiographic variables, including the components of MetS, on atrial conduction times were tested using a stepwise backward elimination method. $p < 0.05$ was considered significant.

Results

The mean age of the patients with MetS was 32.9 ± 5.7 years and that of the controls was 31.6 ± 5.3 years. The clinical and laboratory findings of the subjects are shown in table 1. The 2 groups were similar with regard to age, sex, a family history of coronary artery disease and smoking status ($p > 0.05$). Heart rate, BMI, waist circumference and systolic and diastolic blood pressure were significantly higher in the patient group than in the control group ($p < 0.05$). Echocardiographic characteristics including the LA total and phasic volumes of subjects are shown in table 2. The heart rate of the patients during the examination was between 60 and 80 bpm. LV septum and posterior wall thickness, LVMI corrected for height and LA diameter were increased in patients with MetS (all $p < 0.05$). Although MetS patients had a greater mitral A velocity, LV E/Em ratio and LV Am, and a lower E/A ratio and LV Em, these measurements were within the normal range. The MetS group had a greater LA maximum ($p = 0.03$), preatrial contraction ($p = 0.001$) and active emptying volume ($p = 0.001$) than the control group, but the passive emptying fraction was lower ($p = 0.001$).

The PA intervals are summarized in table 3. The PA intervals measured on the basal LV PAlateral ($p < 0.001$), PAseptal ($p = 0.001$) and right ventricular PAtricuspid ($p = 0.008$) were longer in the MetS patients. Patients with MetS had higher interatrial EDs than controls (21.0 ± 11.5 vs. 12.3 ± 10.4, $p < 0.001$) and also higher intra-atrial EDs than controls (10.3 ± 6.3 vs. 7.4 ± 5.5, $p = 0.003$; fig. 1a). The Pd was significantly higher in the MetS patients ($p <$

Table 1. Clinical and laboratory characteristics of the study population

	Controls (n = 67)	MetS patients (n = 87)	p value
Age, years	31.6±5.3	32.9±5.7	0.128
Male gender	40 (60)	54 (62)	0.868
BMI	25.9±4.4	30.9±4.9	<0.001
Diabetes mellitus	2 (3)	7 (8)	0.31
Smoking	22 (33)	39 (45)	0.139
CAD family history	24 (36)	46 (53)	0.06
Obesity	13 (19)	49 (56)	<0.001
SBP, mm Hg	124±13	132±15	<0.001
DBP, mm Hg	79±7	86±9	<0.001
Heart rate, bpm	76±12	82±12	0.003
Total cholesterol, mg/dl	181.6±28.6	196.7±32.1	0.003
LDL, mg/dl	107.6±25.1	119.8±28.1	0.005
VLDL, mg/dl	22±10.8	37.6±18.5	<0.001
Components of MetS			
Waist circumference, cm	90.3±9.3	105.0±10.6	<0.001
Hypertension	14 (19)	52 (59)	<0.001
Fasting blood glucose, mg/dl	89.3±6.9	97.5±11.9	<0.001
Triglycerides, mg/dl	121.3±51.9	188.9±89.2	<0.001
HDL, mg/dl	50.7±10.2	39.3±6.3	<0.001

Values are given as n (%) or means ± SD. CAD = Coronary artery disease; DBP = diastolic blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SBP = systolic blood pressure; VLDL = very-low-density lipoprotein.

0.001; fig. 1b). In a subgroup analysis, none of the aforementioned parameters was significantly different between male and females or between subjects with and without diabetes mellitus.

In the univariate correlation analysis, the interatrial ED was significantly correlated with Pd ($r = 0.358$, $p < 0.001$), LA Vp ($r = 0.285$, $p < 0.001$), LA active emptying volume, ($r = 0.327$, $p < 0.001$), LA passive emptying fraction ($r = -0.267$, $p = 0.001$) and E/A ratio ($r = -0.236$, $p = 0.003$). The intra-atrial ED was correlated with Pd ($r = 0.197$, $p = 0.014$), LA Vp ($r = 0.210$, $p = 0.009$), LA active emptying volume, ($r = 0.239$, $p = 0.003$) and LA passive emptying fraction ($r = -0.239$, $p = 0.003$).

In the multivariate linear regression analysis, a model adjusted for age, gender, E/A ratio, LA active emptying volume and the presence of MetS was used. The presence of MetS, LA active emptying volume and LV E/A ratio remained as the independent correlates of interatrial ED ($R^2 = 0.248$, $\beta = 0.24$, $p = 0.002$; $\beta = 0.30$, $p = 0.001$ and $\beta = -0.17$, $p = 0.025$, respectively).

The coefficient of variance (CV) values for intraobserver variability were 5.7% for Vmax, 5.6% for Vmin, 5.5% for Vp and 5.5% for PAlateral, 5.8% for PAseptal and 5.4% for PAtricuspid, respectively. The CV values for

Table 2. Comparison of echocardiographic characteristics (conventional parameters and LA total and phasic volumes) between patients with MetS and controls

	Controls (n = 67)	MetS patients (n = 87)	p value
LV end-diastolic dimension, mm	46.7±4.4	47.6±4.2	0.225
LV systolic dimension, mm	28.6±4.3	28.5±4.3	0.920
Septum thickness, mm	9.1±1.1	9.8±1.2	0.001
Posterior wall thickness, mm	8.9±1.1	9.7±1.1	<0.001
LV ejection fraction, %	68±4	69±5	0.570
LVMI, g/m^2	77.2±16.3	80.8±14.3	0.152
LVMI, g/m	85.8±21.3	98.1±20.5	<0.001
LA diameter, mm	31.5±4.9	33.9±3.7	0.002
Mitral E velocity, cm/s	83.7±11.4	79.5±16.6	0.78
Mitral A velocity, cm/s	53.8±10.2	59.0±13.8	0.01
E/A ratio	1.6±0.3	1.4±0.3	0.001
Deceleration time, ms	187.1±18.8	191.8±27.7	0.213
LV E/Em ratio	5.8±1.3	6.5±1.8	0.004
LV Sm, cm/s	9.2±1.5	9.2±1.4	0.814
LV Em, cm/s	14.9±2.8	12.6±2.7	<0.001
LV Am, cm/s	8.2±1.9	9.6±2.1	<0.001
LA maximum volume, ml/m^2	22.1±4.9	23.9±4.9	0.03
LA minimal volume, ml/m^2	6.3±2.6	7.0±2.8	0.105
LA Vp, ml/m^2	11.8±4.2	14.2±4.1	0.001
LA passive emptying volume, ml/m^2	10.3±3.1	9.9±3.6	0.381
LA passive emptying fraction, %	47.2±11.8	41.0±11.2	0.001
LA conduit volume, ml/m^2	22.1±3.2	21.2±3.0	0.09
LA active emptying volume, ml/m^2	5.5±2.5	7.0±2.7	0.001
LA active emptying fraction, %	46.8±13.5	50.0±13.3	0.153
LA total emptying volume, ml/m^2	15.9±3.7	17.0±3.8	0.59

Table 3. Electrocardiographic Pd parameters and PA findings measured by TDI

Electrocardiographic measurements, ms	Controls (n = 67)	MetS patients (n = 87)	p value
Pmax	88.3±11.8	95.3±12.7	0.001
Pmin	59.1±10.7	53.3±11.2	0.001
Pd	29.2±7.4	41.7±10.8	<0.001
PAlateral	74.7±22	89.5±18.8	<0.001
PAseptal	69.6±17.2	78.9±16.6	0.001
PAtricuspid	62.2±14.6	68.6±14.7	0.008
Interatrial ED (PAlateral – PAtricuspid)	12.3±10.4	21.0±11.5	<0.001
Intra-atrial ED (PAseptum – PAtricuspid)	7.4±5.5	10.3±6.3	0.003

interobserver variability were 5.1% for PAlateral, 6.1% for PAseptal and 5.5% for PAtricuspid, respectively.

The intraobserver and interobserver variability for Pmax was 4.3 and 4.8%, respectively. The CV values for intraobserver and interobserver variability were 4.9 and 5.1% for Pmin, respectively.

Discussion

In this study, we found that both intra-atrial and inter-atrial times were greater and LA mechanical function was impaired in MetS patients without atrial arrhythmia.

MetS is highly prevalent in the general population, affecting about 44% of adults according to International Diabetes Federation criteria [4]. It is an important and well-known risk factor for atrial fibrillation (AF). The individual components of MetS are also risk factors for AF [15]. The mechanisms that link MetS to an increased risk of

Fig. 1. a Box plot graph showing the comparison of interatrial ED in the MetS and control groups. Median (horizontal lines), 25th to 75th percentiles (boxes) and 95th percentiles (whiskers). **b** Box plot graph showing the comparison of Pd in the MetS and control groups. Median (horizontal lines), 25th to 75th percentiles (boxes) and 95th percentiles (whiskers).
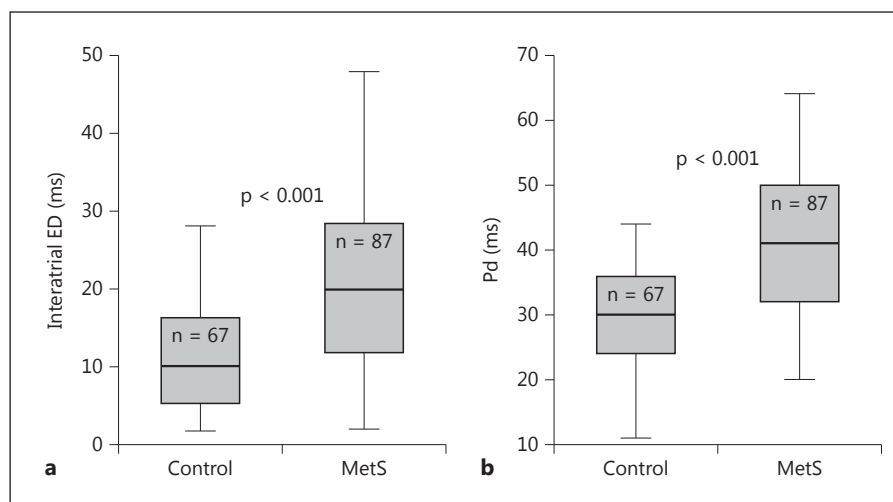
developing AF are not clearly understood [16]. Previous studies demonstrated that MetS is associated with an increase in heart rate, LV hypertrophy, impairment of diastolic function, enlargement of the LA diameter and atrial fibrosis [5, 17–20]. In our study, we found that in the patients with MetS, LA diameter was greater and LA volumes were changed; these factors make for worse LA mechanical functions and diastolic parameters. LA functions are important determinants of LV filling, particularly when LV compliance is reduced. The atrium modulates ventricular filling through its reservoir, conduit and pump functions [21, 22]. In this study, the MetS patients had a greater LA maximum volume, Vp and active emptying volume than the control group. Conversely, LA passive emptying fraction was decreased in the patients with MetS. In addition, in the multivariate regression analysis, the presence of MetS was an independent correlate of interatrial ED besides LV E/A ratio and LA active emptying volume. It has been demonstrated that LA mechanical functions are impaired in hypertensive and diabetic patients [7]. Recently, it was reported that in patients with MetS, LA maximal volume, active emptying volume and fraction are increased but LA passive emptying volume and fraction are decreased [9]. These findings suggest that atrial reserve and pump functions are impaired in patients with MetS.

Although measured diastolic function parameters were within the normal range, there was a significant difference between the 2 groups. The MetS patients had greater mitral A velocity, LV E/Em ratio, LV Am and lower LV Em and E/A ratio. These findings could indicate an early form of diastolic dysfunction. Several studies have found that patients with MetS have LV diastolic dysfunction [17–23]. LV diastolic abnormality leads to afterload

increase in the LA. Thus, LA dilatation and increased LA reservoir function occur due to increased LV stiffness [9].

Atrial conduction time can be measured by both invasive and noninvasive methods [6]. Intra-atrial and interatrial conduction time prolongation and the inhomogeneous propagation of sinus impulses are known electrophysiological characteristics in patients with paroxysmal AF. It has been shown that the prolongation of atrial conduction time, measured by TDI, is an independent predictor of new onset or recurrent AF [24]. In our study, intra-atrial and interatrial EDs were prolonged, and the presence of MetS, LA active emptying volume and LV E/A ratio were independent correlates of interatrial ED. In accordance with these findings, previous studies reported that interatrial and intra-atrial conduction times are increased in patients with impaired fasting blood glucose, type 1 diabetes mellitus and MetS [7, 25, 26].

Prolonged P-wave duration and increased Pd have been reported to be associated with an increased risk for AF [27]. We have found that Pmax and Pd were significantly higher in patients with MetS. Similarly, in another study, Pmax and Pd were significantly higher in MetS patients [28]. Several studies have demonstrated that Pmax and Pd were significantly higher in patients with diabetes mellitus and hypertension [7, 29, 30]. Therefore, in our study, we confirmed the prolongation of atrial electrical activation by using electrocardiography to measure Pd.

The limitations of this study included patients who were not followed prospectively for arrhythmic episodes. The effects of drug therapy on study parameters could not be investigated as the medical therapy of individuals was not altered. Further studies with follow-up are necessary to investigate whether AF occurs in MetS patients with

prolonged inter- and intra-atrial electromechanical duration. The interatrial conduction time was not investigated by invasive electrophysiological techniques. Another limitation was that the study population was relatively small.

Conclusion

This study showed that LA mechanical functions were impaired and intra-atrial and interatrial electromechanical durations prolonged in MetS patients. These findings suggest that MetS may lead to atrial electrical remodeling.

Therefore, atrial arrhythmias may develop due to impaired LA functions. Interatrial ED is a simple and highly reproducible method that can predict AF in patients with MetS. Prospective studies are needed to investigate the relation between intra-atrial and interatrial EDs, LA mechanical functions and future development of AF.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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