ORIGINAL ARTICLE

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Left Ventricular Structural and Functional Changes in the Metabolic Syndrome

To test the hypothesis that the cardiac structural and functional abnormalities of the metabolic syndrome (MS) are independent of body mass index (BMI), 160 untreated patients (aged 47±1 years [mean ± SEM], 53% male) underwent 2-dimensional echocardiography and tissue Doppler imaging and evaluation for MS. Participants with MS and controls were similar in age, BMI, and ejection fraction, but those with MS had greater left ventricular relative wall thickness (RWT) (0.43±0.008 vs 0.39±0.005, P<.001), reduced midwall fractional shortening (MFS) (13%±0.3% vs 14.2%±0.3%, P<.05), and reduced peak mitral annular velocity (Em) (9.9±0.5 vs 12.3±0.5 cm/sec, P<.01) than controls. There was a linear relationship between the number of features of MS and Em velocity (P<.001), RWT (P<.001), and MFS (P<.05). In a stepwise multiple regression analysis adjusting for likely determinants, MS was an independent predictor of Em in addition to age and nonindexed left ventricular mass. MS is associated with left ventricular concentric remodeling and reduced systolic and diastolic function independent of BMI. J Cardiometab Syndr. *2009;4:81–88.* ©*2009 Wiley Periodicals, Inc.*

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The presence of the metabolic syndrome (MS) has a significant impact on mortality and is a risk factor for cardiovascular and coronary heart disease.[1] Some of the key components of the syndrome—obesity, hypertension, and insulin resistance—are linked to the development of heart failure.[2] While hitherto heart failure had been usually considered in terms of systolic failure with a reduced ejection fraction, there is growing appreciation that diastolic dysfunction, which has been relatively neglected in comparison with abnormalities in systolic function, may also play a significant role. Approximately half the patients presenting with signs and symptoms of heart failure have a normal left ventricular ejection fraction but an abnormality in the diastolic properties of the left ventricle, and a history of hypertension is common in such patients.[3,4] Left ventricular diastolic dysfunction usually precedes systolic dysfunction[5,6] characterized by abnormal relaxation in the early stages.[7] Diastolic dysfunction can be assessed by tissue Doppler imaging (TDI), which allows the determination of myocardial systolic and diastolic velocities in the myocardium. During normal left ventricular relaxation, the peak early diastolic mitral annular velocity (Em) recorded by TDI is greater than mitral late diastolic velocity (Am), which is generated by left atrial contraction. In the healthy heart, the Em/Am ratio is >1 and is reversed in left ventricular diastolic dysfunction.[8]

A cross-sectional community survey in Minnesota showed that some one-quarter of the population older than 45 years has diastolic dysfunction predictive of all-cause mortality.[4] Diastolic dysfunction is also common in the hypertensive population, even in the absence of left ventricular hypertrophy (LVH), and has been documented in normotensive men with well-controlled type 2 diabetes.[9] A recent study of patients with treated MS (92% diabetic) compared with controls showed a significant relationship between subclinical left ventricular systolic and diastolic dysfunction and the degree of metabolic burden; these changes were associated with reduced cardiorespiratory fitness.[10] The effects of MS on cardiac structure and function have been investigated previously in selected populations.[11–14] The aim of our study was to examine cardiac abnormalities in MS using TDI in an unselected population referred for assessment of high blood pressure (BP).

Methods

Study Population. We studied 160 consecutive untreated patients (aged 46±1 years [mean ± SEM], 53% male) referred for BP assessment. Patients with diabetes, clinical or electrocardiographic evidence of coronary heart disease, valvular disorders, heart failure, arrhythmias, or renal impairment and those with secondary causes of hypertension were excluded. The patients had never received antihypertensive treatment, other vasoactive drugs, or hormonal preparations. Diagnosis of MS was based on the presence of ≥3 of the criteria established by the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III 2001 guidelines[15]: waist circumference >101 cm (men) or >88 cm (women); fasting triglycerides >1.7 mmol/L; high-density lipoprotein cholesterol

<1.0 mmol/L (men) or <1.3 mmol/L (women); clinic BP ≥130/≥85 mm Hg; and fasting plasma glucose ≥6.1 mmol/L. In addition, we studied the impact of lowering the fasting plasma glucose threshold to ≥5.6 mmol/L, according to the revised NCEP ATP 2005 guidelines.[16]

Weight and height were measured in each patient and body mass index (BMI) was calculated as kg/m^2. Waist circumference was measured at the midpoint between the bottom of the rib cage and the top of the iliac crest at minimal respiration. Fasting total cholesterol, triglycerides, high-density lipoprotein cholesterol, glucose, renal function, and electrolytes were measured by routine laboratory methods. Clinic BP was measured using an automated digital oscillometric monitor (Omron Model HEM 705-CP; Omron Corporation, Tokyo, Japan). All participants underwent 24-hour ambulatory BP monitoring using validated oscillometric devices (SpaceLabs, Issaquah, WA). BP was recorded every 30 minutes between the hours of 6 AM and midnight and hourly from midnight to 6 AM.

Participants gave informed consent; the study was approved by the local institutional ethics committee, and it complied with the Declaration of Helsinki.

Echocardiography. Ultrasonographic echocardiography was performed by an experienced cardiosonographer blinded to the clinical details of the patients and using an Agilent 5500 cardiac ultrasonography system with color flow imaging and TDI capabilities and equipped with 2.5- and 3.5-MHz Philips Probe transducers (Andover, MA). The images of the left ventricle were obtained from the parasternal view and apical windows with the patient in the left lateral decubitus position. Using 2-dimensional echocardiography at the parasternal view, left ventricular end-systolic dimension and left ventricular end-diastolic dimension together with interventricular septum thickness and posterior wall thickness were determined as described previously[17] Left ventricular mass (LVM) was calculated by the method of Devereux, applying the Penn convention,[18] indexed to height$^{2.7}$ and body surface area to determine left ventricular mass index (LVMI). Relative wall thickness (RWT) was calculated as the sum of septal and posterior wall thickness divided by left ventricular end-diastolic dimension. Ejection fraction was calculated by the method of disc summation based on Simpson's rule. Left ventricular systolic function was assessed as midwall shortening based on mathematical models.[19]

Transmitral inflow velocities were measured from the apical 4-chamber view by pulsed-wave Doppler, with the sample volume placed at the tips of mitral leaflets. The ratio between peak early (E) and late (A) transmitral flow velocities (E:A), isovolumic relaxation time (IVRT; time between the closing artifact of the aortic valve and the earliest detection of transmitral flow), and deceleration time of the E velocity (DT, time elapsed between peak E velocity and the point where the extrapolated deceleration slope of the E velocity crosses the zero baseline) were obtained. Myocardial tissue velocities were obtained using TDI from the apical 4-chamber view with the sample volume placed at the lateral mitral annulus. The peak velocities at the lateral annulus and early diastolic (Em) and late diastolic (Am) velocities were measured, and the ratios E:Em and Em:Am calculated. The estimation of left ventricular filling by the TDI method has been shown to be superior to the transmitral flow velocities.[8]

Statistical Analysis. The statistical analysis was performed with JMP version 5.0 (SAS for Windows, SAS Institute, Cary, NC). Power calculations based on experience with the same methodology indicated that a group size of ~140 to 160 would be required to detect a 2-cm/sec difference in Em and a 1% difference in midwall fractional shortening with $1-\beta$ of 90%. Results are presented as mean ± SEM for continuous data and percentages for categorical data. Significance was assumed at $P<.05$. Differences between means were analyzed using the Wilcoxon rank sum test for continuous variables and chi-square for categorical data. Analysis of covariance was used to assess differences between groups after adjustment for age, sex, and BMI. The relationship between various clinical parameters was analyzed using Spearman Rho correlation analysis. To evaluate the role of MS as in independent predictor of left ventricular structure and function, stepwise multiple regression analysis was performed. For early myocardial velocity, Em was the dependent variable, and the independent variables included age, sex, BMI, systolic and diastolic BP, heart rate, RWT, nonindexed LVM, the presence of MS (as a dummy variable by assigning "1" to MS patients and "0" to controls), and features of the syndrome including waist circumference, high-density lipoprotein cholesterol, triglycerides, and plasma glucose. For midwall fractional shortening, the independent variables were similar to those used for Em, but LVM was excluded from the independent variables. For nonindexed LVM, the same model was used as for midwall fractional shortening, except RWT was removed from the independent variables in the model. The analysis was also repeated after removing MS from the model.

Results

The clinical characteristics of the study population categorized according to the presence of MS are presented in Table I. The 2 groups were similar in age, BMI, and sex ratio (Table I). As expected, those with MS had significantly higher clinic BP, larger waist circumference, raised triglycerides, lower high-density lipoprotein cholesterol, and higher fasting plasma glucose. The overall prevalence of MS according to the NCEP ATP III criteria was 28% in our study population, with no statistical difference in prevalence between men (32%) and women (25%). The prevalence of MS increased to 35% by using the NCEP ATP 2005 modified criteria (fasting glucose >100 mg/dL). Because of the study design (enrollment of participants for assessment of high BP), the prevalence of increased BP (clinic BP

≥135/85 mm Hg) was the most common feature in the MS patients (89% vs 58%, $P<.001$), followed by increased waist circumference (87% vs 30%, $P<.0001$), raised triglycerides (64% vs 18%, $P<.001$), low high-density lipoprotein cholesterol (48% vs 13%, $P<.0001$), and high glucose (36% vs 6%, $P<.0001$), compared with controls. While clinic BP levels were significantly higher in patients with MS, there was no difference in 24-hour ambulatory BP between the 2 groups (Table I). There was a significantly higher percentage of patients (44% vs 27%, $P<.05$) with MS who exhibited a white-coat effect (clinic systolic BP ≥20 mm Hg and/or clinic diastolic BP ≥10 mm Hg higher than daytime 24-hour ambulatory BP values) compared with the controls.

While LVM was higher in MS patients, the LVMI was similar between the 2 groups (Table II). However, there was a greater degree of concentric remodeling in the MS patients, as shown by a significantly higher RWT (Table II). With regard to left ventricular systolic function, midwall fractional shortening was significantly reduced in patients with MS despite a similar ejection fraction (Table III). Diastolic function was impaired in patients with MS, as shown by significantly reduced Em and Em:Am ratio in the MS patients, although the Am was similar between the 2 groups (Table III). The DT was prolonged in the MS patients, but the differences in transmitral E and A velocities, E:A ratio, and IVRT did not achieve statistical significance (Table III). Using the modified NCEP ATP 2005 criteria, the results did not change; MS patients had increased nonindexed LVM (165±7 vs 147±4 g, $P<.01$) and RWT (0.43±0.01 vs 0.40, $P<.01$) and reduced midwall fractional shortening (13%±0.2% vs 14%±0.2%, $P<.01$) and Em (10±0.5 vs 12±0.5 cm/sec, $P<.05$), with no significant difference in LVMI.

We also analyzed the contribution of individual components of MS to both systolic and diastolic dysfunction. Em was reduced in patients with raised BP (10.6±0.7 vs 12.5±0.4 cm/sec, $P<.05$), increased waist circumference (10±0.6 vs 12±0.5 cm/sec, $P<.05$), and high triglycerides (10±0.5 vs 12±0.7 cm/sec, $P<.01$) but not in those with reduced high-density lipoprotein cholesterol (10.5±0.5 vs 12±0.6 cm/sec, $P=.28$) or high glucose levels (11.9±0.5 vs 11.3±0.7 cm/sec, $P=.29$). Midwall fractional shortening was reduced, with increased waist circumference (13.5%±0.2% vs 14.5%± 0.2%, $P<.05$) and high glucose levels (12.9%±0.3% vs 14%±0.2%, $P<.05$); there was no relationship with raised BP (13.9%±0.3% vs 14%±0.2%, $P=.66$), reduced high-density lipoprotein cholesterol (13.8%±0.3% vs 14%±0.2%, $P=.7$), or raised triglyceride levels (13.7%±0.28% vs 14%±0.20%, $P=.55$).

MS patients more frequently exhibited a white-coat effect on 24-hour BP monitoring compared with controls; thus, we explored the relationship between the white-coat effect and obesity. After adjusting for age, sex, and clinic systolic BP, BMI was related negatively ($\beta=-0.72$, $P<.001$) and waist circumference positively with the white-coat effect ($\beta=0.53$, $P<.001$). We also analyzed the data after excluding those with the white-coat effect and found similar results as in the overall population. MS

Table I. Clinical Characteristics of Study Population Categorized by the Metabolic Syndrome (N=160, mean ± SEM)

	Metabolic Syndrome		
	+ (n=46)	− (n=114)	*P* value
Age (y)	47±2	47±1	ns
Sex (M/F)	25/21	52/62	ns
Current smokers (%)	25	21	ns
Height (cm)	173±2	168±1	<.001
Weight (kg)	80±2	94±2	<.0001
BMI (kg/m^2)	30±0.6	30±0.7	ns
Waist circumference (cm)	104±2	90±1	<.0001
Clinic systolic BP (mm Hg)	161±2	150±2	<.001
Clinic diastolic BP (mm Hg)	94±1	89±1	<.01
24-Hour systolic BP (mm Hg)	134±2	135±1	ns
24-Hour diastolic BP (mm Hg)	82±1	82±1	ns
Daytime systolic BP (mm Hg)	142±2	143±2	ns
Daytime diastolic BP (mm Hg)	88±1	89±1	ns
Nighttime systolic BP (mm Hg)	118±2	121±2	ns
Nighttime diastolic BP (mm Hg)	70±2	71±1	ns
Heart rate (beats/min)	68±1	70±2	ns
Triglycerides (mg/dL)	212±18	117±8	<.001
HDL cholesterol (mg/dL)	44±1	57±1	<.0001
Fasting glucose (mg/dL)	101±2	92±1	<.001
Total cholesterol (mg/dL)	206±6	192±3	<.05
Uric acid (mg/dL)	6.4±0.3	6.3±0.7	<.05
Creatinine (mg/dL)	0.99±0.03	0.97±0.01	ns

Abbreviations: BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein.

Table II. LV Structural Characteristics in Patients With and Without the Metabolic Syndrome (N=160, mean ± SEM)

	Metabolic Syndrome		
	+ (n=46)	− (n=114)	*P* value
LV mass (g)	164±7	149±4	<.05
LV mass index (g/m$^{2.7}$)	39±2	37±1	ns
LV mass index (g/m^2)	82±4	78±2	ns
Relative wall thickness	0.43±0.008	0.39±0.005	<.05
Left atrial size (cm/height)	2.2±0.04	2.1±0.03	.07

Abbreviation: LV, left ventricular.

Table III. Functional Characteristics of the Study Population Categorized by the Metabolic Syndrome (N=160, mean ± SEM)

	Metabolic Syndrome		
	+ (n=46)	− (n=114)	*P* value
Ejection fraction (%)	62±0.8	63±0.5	ns
Mitral A (cm/sec)	66±2	66±1	ns
Mitral E (cm/sec)	67±2	73±1.5	ns
Mitral E:A velocity ratio	1.02±0.03	1.1±0.03	ns
Isovolumic relaxation time (ms)	90±2	91±2	ns
E deceleration time (ms)	194±4	186±2.5	<.05
TDI Am (cm/sec)	11.8±0.4	11.9±0.2	ns
TDI Em (cm/sec)	9.9±0.6	12.3±0.5	<.001
TDI Em:Am velocity ratio	0.87±0.06	1.1±0.04	<.01
E:Em	7.4±0.4	6.5±0.2	<.05
Midwall fractional shortening (%)	13±0.3	14.2±0.3	<.05

Abbreviations: Am, late diastolic velocity; Em, early diastolic velocity; TDI, tissue Doppler imaging.

patients still had significantly reduced Em (10±0.6 vs 12.5±0.5 cm/sec, $P<.05$) and midwall fractional shortening (13%±0.4% vs 14%±0.2%, $P<.05$) and increased RWT (0.41±0.002 vs 0.40±0.001, $P<.01$) and nonindexed LVM (172±8.0 vs 147±4.6 g, $P<.01$) compared with the controls. These differences remained significant after adjusting for age, sex, and BMI.

Because 89% of persons with MS had hypertension, vs 58% of the controls, we excluded normotensive patients (those with ambulatory daytime BP values <135/85 mm Hg) in a subanalysis. The MS patients (n=41) had reduced Em (9.7±0.5 vs 12±0.5 cm/sec, $P<.01$) and midwall fractional shortening (13%±0.2% vs 14%±0.2%, $P<.05$) and increased RWT (0.44±0.01 vs 0.39±0.01, $P<.01$) and nonindexed LVM (170±7 vs 150±4 g, $P<.01$) compared with the controls (n=87). The results were unchanged when adjusted for age, sex, and BMI.

There was no significant interaction between the number of features of MS and age, sex, or BMI. In the whole cohort, there was a significant linear relationship between the number of components of MS and the reduction in Em ($P<.0001$) and midwall shortening ($P<.01$) and the increase in RWT ($P<.0001$), which remained significant after adjusting for age, sex, and BMI (Figure 1). While there was a linear relationship between the number of features of MS and left atrial size ($P<.01$) and nonindexed LVM ($P<.05$), the trend was no longer significant when adjusted for confounding variables. There was no significant relationship between LVMI and number of features of MS.

In the entire population, there was a significant relationship between Em and waist circumference, but not with BMI (Figure 2). Em was associated with age ($r=-.49$, $P<.0001$), clinic systolic ($r=-.29$, $P<.001$) and diastolic ($r=-.25$, $P<.01$) BP, and triglycerides ($r=-.20$, $P<.01$), but not with high-density cholesterol or fasting glucose (Table IV). Em was associated with left atrial size ($r=-.37$, $P<.0001$), LVMI ($r=-.21$, $P<.01$), and RWT ($r=-.19$, $P<.01$) and weakly with midwall fractional shortening ($r=.15$, $P=.06$) (Table IV). Similar results were observed for the Em:Am ratio. The only significant univariate associations of E:Em were with age ($r=.19$, $P<.01$), clinic systolic BP ($r=.18$, $P<.01$), and left atrial size ($r=.24$, $P<.01$).

LVMI was significantly associated with waist circumference ($r=.34$, $P<.0001$), triglycerides ($r=.20$, $P<.01$), fasting plasma glucose ($r=.17$, $P<.05$), and diastolic BP ($r=.16$, $P<.05$), with no significant association with systolic BP, heart rate, high-density lipoprotein cholesterol, or BMI. Midwall shortening was significantly associated with individual features of MS including waist circumference ($r=-.47$, $P<.0001$), high-density lipoprotein cholesterol ($r=.35$, $P<.0001$), triglycerides ($r=-.20$, $P<.01$), and fasting plasma glucose ($r=-.28$, $P<.001$) but not with BP or BMI. RWT was significantly associated with systolic BP ($r=.22$, $P<.01$) and triglycerides ($r=.17$, $P<.05$), with no significant relationship with diastolic BP, heart rate, high-density lipoprotein cholesterol, waist circumference, or fasting plasma glucose.

In a stepwise multiple regression analysis, the only independent predictors of Em were age ($P<.0001$), the presence of MS ($P<.001$) and nonindexed LVM ($P<.05$) ($R^2=.32$, $P<.0001$). On removing MS from the equation, age, BP, and waist circumference were the only independent determinants of Em. For nonindexed LVM, the only independent determinants were sex ($P<.0001$) and waist circumference ($P<.001$) ($R^2=.30$, $P<.0001$), and the results were unchanged when MS was removed from the model. Similar results were observed for midwall fractional shortening, with the only significant predictors being sex ($P<.0001$) and waist circumference ($P<.0001$) ($R^2=.29$, $P<.0001$); there was no change when MS was removed from the model.

Discussion

This study extends previous observations[11–14] on the association between MS and changes in left ventricular geometry, systolic dysfunction, and abnormalities in left ventricular relaxation. The presence of MS emerged as an independent predictor of impaired diastolic function, but not of changes in nonindexed LVM and midwall fractional shortening. However, diastolic impairment was not independent of left ventricular geometric changes, as nonindexed LVM emerged as an independent predictor of diastolic dysfunction.

We found 28% of the study participants to present with MS as defined by NCEP ATP III criteria[15]; the most frequent component in addition to high BP was waist circumference. When we used the modified NCEP ATP criteria[16] to define MS, the prevalence increased to 35%, with similar cardiac morpho-

functional alterations in MS patients as seen when the original NCEP ATP III criteria were used.

In our study, higher RWT, reduced midwall fractional shortening, and diastolic function in the MS patients were not accounted for by age, sex, or BMI, as the groups were similar in respect to these parameters. This was also seen following adjustment in stepwise multiple regression analysis. Previous studies have shown a higher LVMI in MS,[5,19] but the study participants had a significantly higher BMI than the controls in these studies. Our study is unique in that BMI was identical in both groups, which may reflect the marked recent increase in obesity in the Irish population, who are now presenting with increased BP, and the National Obesity Strategy recommending that such persons have BP measured. However, the MS patients in our study were also taller; this highlights the limitation in using BMI as the index of obesity and the reason for using waist circumference for risk assessment. While abdominal obesity is one of the cardinal features of MS, we believe that the constellation of the hemodynamic and metabolic features of MS contributes to the cardiac structural and functional abnormalities in our patients.

We found Em and the Em:Am ratio to be significantly reduced in our MS patients compared with controls, and the presence of MS was an independent predictor of Em. There are conflicting reports regarding the relationship between MS and diastolic dysfunction, with some showing a reduced transmitral E:A ratio in MS[20,13] and others showing no such change.[12,14] However, our findings confirm those of a recent study[11] in which the TDI Em was significantly reduced in patients with MS compared with controls despite no difference in the E:A ratio. One possible explanation is the difference in methodology used to evaluate diastolic function. It is known that the transmitral E:A ratio is not sensitive because it is relatively load-dependent and influenced by age and sex.[8] We used TDI in the present study, in addition to transmitral E:A, and were able to show significantly impaired diastolic function in MS patients. We believe that these early changes are of clinical importance, as Em measured by TDI provides prognostic information incremental to clinical data and standard echocardiographic variables.[21]

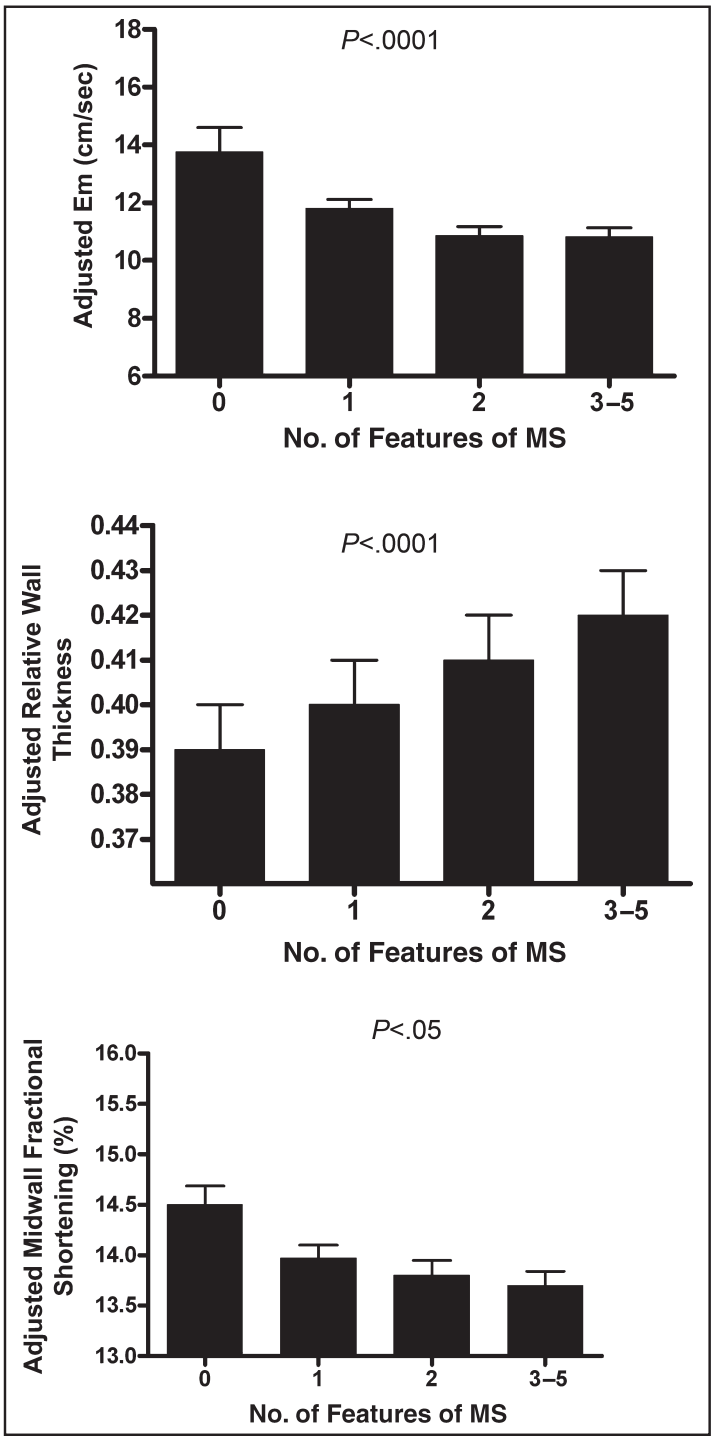

Figure 1. *Relationship between features of the metabolic syndrome (MS) and tissue Doppler imaging peak mitral annular velocity (Em) (top), relative wall thickness (middle), and midwall fractional shortening (bottom) in the study population adjusted for age, sex, and body mass index in the total study population (N=160, mean ± SEM).*

Structural alterations observed in the present study are in agreement with previous observations[12,14] showing elevated LVM and RWT in persons with MS. However, we did not observe any difference in LVMI between the 2

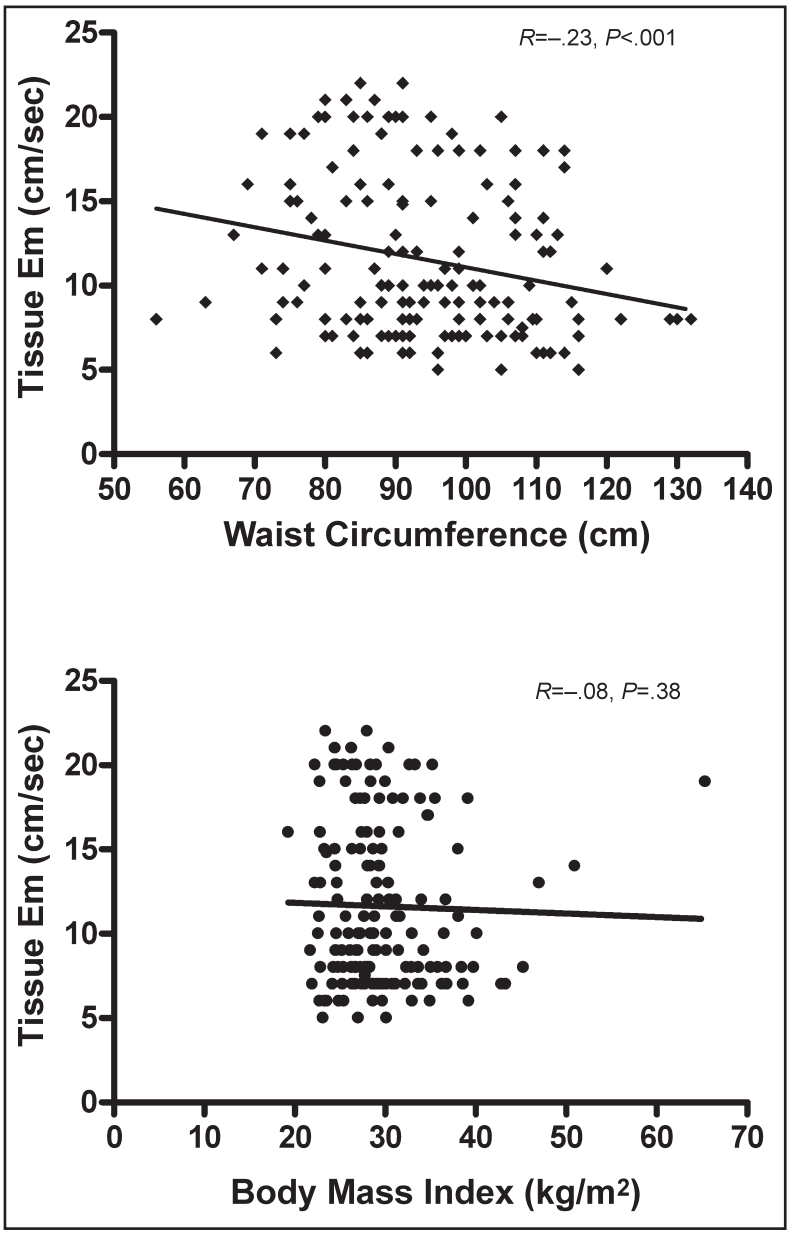

Figure 2. *Relationship between tissue Doppler imaging peak mitral annular velocity (Em) and waist circumference (top) and body mass index (bottom) in the entire study population (N=160, mean ± SE).*

groups. We were able to show reduced systolic function as measured by midwall fractional shortening in MS, confirming the findings in some[12,14] but not all previous studies.[11,14] The differences may be due to different study populations; both Grandi and associates[11] and Cuspidi and colleagues[14] studied hypertensive individuals with MS. While previous studies[12] have shown women with MS to have a higher incidence of LVH, this was not seen in the present study. Because the number of MS patients in our study was small, we did not have enough power to perform analysis in both sexes separately. One can speculate, however, that this difference may be due to the higher BMI observed in the MS patients in the study by Schillaci and associates,[12] whereas in the present study, BMI was identical in the MS and control participants, regardless of sex.

The diastolic dysfunction observed in the current study was independent of systolic dysfunction but not LVM. It is generally accepted that impaired relaxation is frequent when LVH is present and left ventricular relaxation is prolonged when LVM becomes inappropriately high. In the Losartan Intervention For Endpoint Reduction (LIFE) study, antihypertensive treatment and LVH regression were accompanied by parallel improvement of left ventricular active relaxation and passive stiffness.[22] Some recent studies have suggested that left ventricular diastolic dysfunction may precede LVH in hypertensive patients.[23,24] However, the patients in these studies were receiving multiple antihypertensive drugs, and in the latter the prevalence of LVH was only 3%, probably due to antihypertensive treatment. However, as the participants in our study were untreated, the prevalence of LVH was higher, at 15%. This may account for nonindexed LVM emerging as an independent determinant of left ventricular diastolic dysfunction in the present study.

Because our study population was referred for the assessment of high BP, one can argue that the diastolic dysfunction observed in our MS patients is largely driven by increased BP. In the Strong Heart Study,[14] increased BP, even in the normal to high range, was associated with left ventricular geometric alterations and increased LVM. When we excluded normotensive individuals, MS was still associated with increased RWT and nonindexed LVM and impaired systolic and diastolic function, suggesting that the interaction of BP with features of MS—rather than only elevated BP per se—leads to cardiac abnormalities in MS. Our findings suggest that even normal to high BP is an important problem in the context of MS. Therefore, one can speculate that in the presence of MS, a BP value >130/85 mm Hg is as detrimental to the cardiovascular system as traditionally defined hypertension.

One interesting finding in our study was the higher proportion of persons with the white-coat effect in the MS group compared with the controls; however, excluding such patients from the analysis did not alter our findings. There are conflicting data on the

relationship between obesity and white-coat hypertension: one study[25] reports a higher incidence of white-coat hypertension in obese compared with normal-weight persons, and a more recent one[26] shows an inverse relationship between obesity and the white-coat effect on systolic BP. None of these studies have analyzed the relationship between abdominal obesity (waist circumference) and the white-coat effect. This is important, as our results show that while generalized obesity (BMI) is related inversely with the white-coat effect, abdominal obesity (waist circumference) shows a positive association. This further highlights the limitation of using BMI as an index of obesity. The higher prevalence of the white-coat effect in the MS cohort may be attributable to increased sympathetic drive and vascular reactivity in MS.[27] Substances with sympathostimulating effects (leptin, adrenaline, insulin, etc) are also increased in obesity.[28,29]

Table IV. Results of Univariate Analysis Showing Correlation Coefficients Between Tissue E and E:A Velocity with Clinical and Echocardiographic Parameters in the Whole Study Population (N=160)

	E		E:A	
Variable	*R*	*P* value	*R*	*P* value
Age (y)	−.49	.0001	−.50	.0001
BMI (kg/m^2)	.08	.38	.01	.86
Systolic BP (mm Hg)	−.29	.0003	−.27	.0007
Diastolic BP (mm Hg)	−.25	.002	−.29	.0003
Heart rate (beats/min)	−.12	.10	−.25	.002
Waist circumference (cm)	−.23	.001	−.31	.0001
Triglycerides (mmol/L)	−.20	.01	−.21	.001
HDL cholesterol (mmol/L)	.03	.13	.03	.11
Glucose (mmol/L)	−.003	.96	.02	.66
Left atrial size (cm/m)	−.37	.0001	−.37	.0001
LVMI (g/m^2)	−.18	.02	−.21	.006
LVMI (g/m$^{2.7}$)	−.21	.003	−.23	.003
Relative wall thickness	−.19	.01	−.22	.005
Isovolumetric relaxation (ms)	−.36	.0001	−.37	.0001
Deceleration time (cm/sec)	−.54	.0001	−.60	.0001
Midwall fractional shortening (%)	.15	.06	.09	.24

Abbreviations: BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LVMI, left ventricular mass index.

There was a significant linear relationship between the number of features of MS and abnormalities of structure—increased RWT and left atrial size, diastolic dysfunction, reduced Em and Em:Am, reduced systolic function, and reduced midwall fractional shortening—suggesting that increasing severity of MS is accompanied by greater abnormalities. Participants with no metabolic features were all normotensive and, as expected, had normal echocardiographic parameters. Removing normotensive persons from our analysis, however, did not change the results. The largest deterioration appeared to occur when the patients had $\geq$2 features of the syndrome. Thus, even 2 features may suggest early cardiac changes and imply a case for early intervention before the development of the full constellation of the features of MS; higher RWT, reduced midwall fractional shortening, and diastolic dysfunction are independent prognosticators of cardiovascular events.[30–33]

Due to the small sample size and cross-sectional nature of our study, we cannot infer causality between MS and left ventricular abnormalities. However, the strengths of our study include an untreated nondiabetic population without overt cardiovascular disease and an identical BMI between the MS and control groups.

In conclusion, in untreated nondiabetic patients, MS is associated with marked alterations of left ventricular geometry and function independent of age, sex, BMI, and BP. It may be that there is a complex interplay of metabolic and hemodynamic components of MS, with a possible contribution from high sympathetic drive, which leads to cardiac morphofunctional alterations. Therefore, MS may be, in its own right, an important risk factor for both systolic and diastolic heart failure. These data support the view that in persons with MS, in addition to lifestyle measures, early intervention with lipid-lowering and antihypertensive treatment may prevent cardiac damage.

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