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Preclinical Left Ventricular Diastolic Dysfunction in Metabolic Syndrome

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Abstract

Metabolic syndrome (MS) is commonly associated with left ventricular (LV) diastolic dysfunction and LV hypertrophy. We sought to examine whether preclinical LV diastolic dysfunction can occur independent of LV hypertrophy in MS. We recruited 90 consecutive participants with MS and without cardiovascular disease (mean age 46 years, 78% women), and 26 controls (no risk factors for MS; mean age 43 years, 65% women). Participants underwent echocardiography with tissue Doppler imaging. In age- and sex-adjusted analyses, MS was associated with higher left atrial (LA) diameter, higher LV mass, lower E/A ratio, and lower mean e' ($P<0.001$ for all). These associations remained significant after further adjusting for blood pressure, anti-hypertensive medication use, and body-mass index. After adjusting for LV mass, MS remained independently associated with higher LA diameter, lower E/A ratio and lower mean e' ($P\leq0.01$ for all). Specifically, subjects with MS had a 1.8 cm/s lower mean e' compared with controls ($P=0.01$). Notably, differences in mean e' between those with and without MS were more pronounced at younger ages (P for interaction=0.003). In conclusion, MS was associated with preclinical LV diastolic dysfunction independent of LV mass, as reflected by higher LA diameter, lower E/A ratio, and lower mean e'. This suggests that MS can lead to the development of diastolic dysfunction via mechanisms independent of hypertrophy. Differences in diastolic function were more pronounced at younger ages, highlighting the potential importance of early risk factor modification and preventive strategies in MS.

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Keywords

Metabolic syndrome; Left ventricular hypertrophy; Diastolic dysfunction

Metabolic Syndrome (MS) has been associated with subclinical changes in cardiac structure and function, including diastolic dysfunction and left ventricular (LV) hypertrophy.[1] Previous studies have shown that preclinical LV diastolic dysfunction and LV hypertrophy both are strong risk factors for the future development of clinical heart failure, and specifically increase the risk of heart failure with preserved ejection fraction.[2,3] The pathways leading to preclinical LV diastolic dysfunction are diverse, and mechanisms of progression to heart failure poorly understood. In the MS, LV diastolic function and LV hypertrophy appear to worsen in a stepwise fashion with the number of risk factors for MS.[1,4] These findings may account in part for the augmented cardiovascular morbidity and mortality that is associated with MS.[5] Whether these associations are due to age-related changes, hypertension, or other cardiometabolic effects of MS remains unclear. Further, the true prevalence of preclinical diastolic dysfunction in MS and relation to components of the MS are not well defined. We sought to further characterize cardiac structure and function in subjects with and without MS. Specifically, we hypothesized that MS is associated with preclinical diastolic dysfunction, and that this association can occur independent of the hypertrophy. These findings might lend further insight into potential mechanisms by which MS is associated with the eventual development of heart failure.

Methods

We conducted an observational cross-sectional study of consecutive participants with MS who attended outpatient visits at general cardiology, hypertension, obesity and nutrition clinics at Boston Medical Center. MS was defined as meeting 3 or more of the following criteria: (a) increased waist circumference (≥102 cm in men or ≥88 cm in women); (b) increased fasting triglyceride (≥150 mg/dL); (c) high blood pressure (≥130/85 mmHg) or anti-hypertensive therapy; (d) decreased high-density lipoprotein cholesterol (<40 mg/dL in men or, <50 mg/dL in women); (e) impaired fasting glucose (≥100 mg/dL).[6] Controls without MS were recruited at Boston Medical Center, and were defined as meeting none of the 5 criteria for MS. Participants with existing cardiovascular disease (heart failure, LV ejection fraction (LVEF) <50%, coronary artery disease, or valvular heart disease) were excluded from the study.

All participants underwent a comprehensive medical history and physical examination. Resting heart rate, anthropometrics, blood pressure (obtained after 10 min of rest in the sitting position, expressed as the average of 3 consecutive measurements), and fasting blood work were obtained. Hypertension was defined as a systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg and/or current anti-hypertensive therapy. Severe hypertension was defined as taking 2 or anti-hypertensive medications. Diabetes mellitus was defined as a fasting serum glucose level ≥126 mg/dL and/or current medical therapy with an oral hypoglycemic agent and/or insulin. The study was approved by the Boston

University Medical Center Institutional Review Board. All participants provided informed consent prior to study enrollment.

Transthoracic echocardiography was performed with 1–5 MHz transducer and commercial ultrasound system (Philips iE33) by an experienced sonographer. Studies were analyzed off-line using a digital echo interface (Philips XCelera) by a single observer blinded to MS status (NA). Internal dimensions, left ventricle wall thickness, and LVEF (by modified Simpson's rule) were measured according to published recommendations.[7,8]

Left atrial (LA) volume was measured in the apical 2-and 4-chamber views and indexed to body-surface area according to published recommendations.[7,8] Relative wall thickness (RWT) was calculated as the mean of the end-diastolic posterior and septal walls thicknesses, divided by the LV end-diastolic diameter. LV mass was determined by the cubed method and indexed to height to the power of 2.7 to correct for body habitus, and LV hypertrophy defined as LV mass index > 44 $g/m^{2.7}$ in women and >48 $g/m^{2.7}$ in men.[8,9] Pulsed-wave Doppler derived transmitral inflow velocities were obtained in the apical 4-chamber view at a sweep speed of 100 mm/s with the sample volume placed at the mitral valve leaflet tips. Measurements included the transmitral early diastolic (E-wave) and atrial (A-wave) velocities to calculate E/A ratio and E-wave deceleration time (DT).[7,10] Tissue Doppler imaging was used to obtain LV myocardial velocities in the apical 4- chamber view with a sample volume placed at the medial and lateral mitral annulus. Measurements included medial and lateral early diastolic (e') myocardial velocities, and mean e' was calculated as the average of medial and lateral e'. All echocardiographic measurements were averaged over three consecutive cardiac cycles (when available). Repeated measurements of 10 scans showed an intra-observer coefficient of variation of 0.9–4.7%, and an intra-class correlation coefficient of 91–99% for linear measures.

Baseline clinical characteristics and echocardiographic measures were summarized for participants with and without MS. Between-group differences in baseline measures were assessed using two-sample t-tests or Pearson's chi-squared tests as appropriate. The association of MS and measures of cardiac structure and function was assessed using multivariable linear regression. Hierarchical models were constructed, first adjusting for age and sex, and then further adjusting for systolic blood pressure, the use of anti-hypertensive medications and body-mass index (BMI). Lastly, analyses examining measures of diastolic function that remained associated with MS were further adjusted for LV mass. Because age is known to be a strong determinant of diastolic function,[11] we tested for statistical interaction between age and MS.

In exploratory analyses, we examined the association of the total number of MS risk factors and echocardiographic parameters for the subgroup of individuals with MS using one-way ANOVA. We also examined the association of different components of MS and measures of cardiac structure and function in participants with MS. Stepwise multivariable regression models were constructed, using forward selection with retention of variables at a $P<0.05$, forcing age and sex. Models were also repeated using backward elimination. Analyses were performed using STATA version 10.1 (Stata Corp, College Station, TX, USA) software.

Results

A total of 116 subjects were enrolled in our study, including 90 subjects with MS (mean age 46 years, 78% women), and 26 controls without MS (mean age 43 years, 65% women). Baseline characteristics by group are displayed in Table 1. Overall, subjects with MS had a worse cardiovascular risk factor profile, including higher blood pressure, BMI, and dyslipidemia. Fifty seven percent of subjects with MS met at least four of the established criteria.

Echocardiographic measures for control and MS groups are presented in Table 2. While there were small differences in LV dimensions and LVEF between groups, subjects with MS have greater LV mass, with 28% and 24% meeting criteria for concentric remodeling or concentric hypertrophy, respectively[8]. None of the subjects in the control group had concentric hypertrophy, and two participants had concentric remodeling. Subjects with MS also had worse measures of diastolic function, including higher left atrial diameters, lower E/A ratio and lower mean e'. Specifically, 34% of subjects with MS had a mean e' < 8 cm/s, whereas only 13% of control subjects had a mean e' < 8 cm/s.

In age- and sex- adjusted analyses, MS was associated with echocardiographic features of diastolic dysfunction, including higher LA diameter, higher LV wall thickness, higher LV mass, lower E/A ratio, and lower mean e' ($P<0.001$ for all, Table 3). These associations of MS and LA diameter, relative wall thickness, E/A ratio, and mean e' appeared to be independent of blood pressure, anti-hypertensive medication use, and BMI ($P<0.05$ for all; Table 3). After additional adjustment for LV mass, MS remained independently associated with lower E/A ratio ($P=0.002$) and lower mean e' ($P=0.01$; Table 3). A total of 32 participants with MS (34%) had a mean e' < 8 cm/s, of whom 15 (47%) had low mean e' in the absence of LV hypertrophy criteria.

While LA diameter was significantly higher in MS in multivariable-adjusted models, LA volume when indexed to body-surface area was not significantly associated with MS after accounting for blood pressure and BMI ($P>0.05$).

In sensitivity analyses including only white subjects (45 MS, 21 controls), primary results were not materially different. Similarly, results did not change appreciably after adjusting for smoking status or diabetes mellitus status.

Among the different echocardiographic measures that were found to be significantly associated with MS, age was a significant predictor of A, E/A ratio and mean e'. To further explore whether age is an effect modifier in the associations between MS and diastolic function measures, we tested for an age interaction term. There was a significant interaction between age and MS as predictors of mean e' ($P=0.003$), suggesting that although MS was associated with lower mean e' at any age, this difference was most pronounced at younger ages (Figure 1). For example, for a man age 30 with a systolic blood pressure of 120 mmHg and BMI of 30, the predicted mean e' was 11.0 cm/s in individuals with MS and 14.3 cm/s in those without MS. In contrast, at age 50 years for the same clinical criteria, the predicted mean e' was 9.3 cm/s with MS, and 10.3 cm/s without MS.

In exploratory analyses, we examined the association of the total number of MS risk factors and echocardiographic parameters within individuals with MS. The number of MS risk factors was associated with E/A ratio (P=0.003) and mean e' (P=0.03), but not other echocardiographic parameters. We further examined the association of individual components of the MS and echocardiographic measures using stepwise selection models. In multivariable analyses, increased waist circumference and lower high-density lipoprotein cholesterol were independently associated with increased LV mass after adjustment for age and sex (P<0.05 for all). Elevated triglycerides were associated with mean e' after adjustment for age and sex.

Discussion

We found that MS was associated with preclinical LV diastolic dysfunction as reflected by higher LA diameter, lower E/A ratio, and lower mean e' in a sample of individuals without existing cardiovascular disease. Notably, this association was independent of other clinical factors commonly associated with diastolic dysfunction, including age, blood pressure, and LV mass.[3,10,11] These findings suggest that MS can lead to the development of diastolic dysfunction via mechanisms that are independent of hypertrophy, and potentially lend further insights into the increased cardiovascular risk observed in MS.[5,12] Further, we found that age acts as an effect modifier, such that differences in diastolic function in participants with and without MS were more pronounced at younger ages. This may be due to bigger differences in subclinical cardiovascular disease at younger ages, which attenuate with increasing age and the development of other comorbidities. The presence of preclinical diastolic dysfunction at younger ages highlights the importance of future studies focused on early risk factor modification and preventive strategies in MS.

Our results are consistent with prior studies showing an association of MS and increased LV mass.[13–15] While elevated blood pressure is one of the important components of MS, and hypertension is known to lead to increases in LV mass,[16] we found that the association of MS and increased LV mass was independent of blood pressure. Further, in exploratory analyses, we show that measures of obesity and lower high-density lipoprotein cholesterol influence LV mass in individuals with MS. These results showing the association of metabolic disease and increased LV mass are consistent with prior studies looking at MS or its risk factors that have linked increases in LV mass with dyslipidemia[17] and obesity.[18]

A number of previous studies have demonstrated subclinical cardiac remodeling in MS[1,19] or components thereof, including insulin resistance, diabetes, and obesity.[20–22] Some previous studies of MS have largely focused on LA dimensions, mitral E/A ratios and E deceleration time as metrics of diastolic function.[1,19] We now extend these findings and show an association of MS with lower myocardial relaxation velocity as measured by tissue Doppler. Tissue Doppler indices have previously been shown to be relatively unaffected by changes in loading conditions, particularly in the presence of diastolic dysfunction,[7] and thus are advantageous in this patient population, where subclinical diastolic dysfunction is more common.

We specifically show that the association of MS and lower global e' is independent of blood pressure, LV mass, age, and other clinical factors.[1] Importantly, while LV hypertrophy may lead to diastolic dysfunction,[16] our results suggest that MS can lead to impaired myocardial relaxation independent of changes in LV mass. In this regard, it is noteworthy that nearly half of individuals with MS who had diastolic dysfunction (mean e' < 8 cm/s) did not have LV hypertrophy. Interestingly, previous studies have shown diastolic dysfunction in diabetics to be associated with diffuse myocardial fibrosis, which supports our findings

We found that left atrial dimension was higher in those with MS compared with controls, while there was no difference in left atrial volume even after indexing for body size. This is consistent with the mild degree of diastolic dysfunction seen in this preclinical sample, where definitive left atrial enlargement may not have developed yet. Other studies of preclinical disease have demonstrated changes in tissue Doppler velocities, which may reflect early myocardial changes in the absence of significant left atrial remodeling.[23]

Higher BMI has previously been found to be associated with worse LV diastolic function independent of LV mass in a population-based study where MS was not specified.[24] However, after adjusting for BMI, our results remained robust, and suggest that obesity alone does not account for the association of MS and diastolic dysfunction.

The pathophysiological mechanism by which MS can lead to abnormalities in LV diastolic function is not well understood. In mouse models of diet-induced MS, increased myocardial oxidative stress has been implicated in the development of diastolic dysfunction, and was associated with both hypertrophy and fibrosis of the myocardium.[25] Animal models of insulin resistance, hypertension, or dyslipidemia have also implicated the development of cardiac fibrosis, abnormal intracellular calcium handling,[25,26] cardiomyocyte lipotoxicity, mitochondrial dysfunction, impaired endothelial blood flow, increased vascular stiffness, and inflammation.[27] While mechanistic inferences cannot be drawn from our observational study, these results support the notion that metabolic heart disease can lead to impaired myocardial relaxation in the absence of LVH. Further studies are needed to elucidate potential mechanisms and potential therapeutic targets.

Several limitations deserve mention. First, ours is a cross-sectional observational study, and causal inferences are therefore limited. Second, healthy controls were selected based on the absence of any MS criteria. This resulted by design in baseline differences of clinical characteristics between participants with and without MS. It is therefore possible that residual confounding could in part account for our findings. Lastly, healthy controls in our sample were predominantly white, whereas nearly half of participants with MS were black, an important point since LV hypertrophy,[28] and diastolic dysfunction, are more prevalent among blacks. Our sample size was not powered to examine racial differences, however, the primary study results were not materially different in sensitivity analyses including only whites. In our study LV mass was indexed to height to the power of 2.7,[9] which has been shown to be more applicable in obese populations,[29] however other methods of indexing may have resulted in different findings. Lastly, exploratory analyses examining individual components of MS with echocardiographic traits were limited due to a modest sample size.

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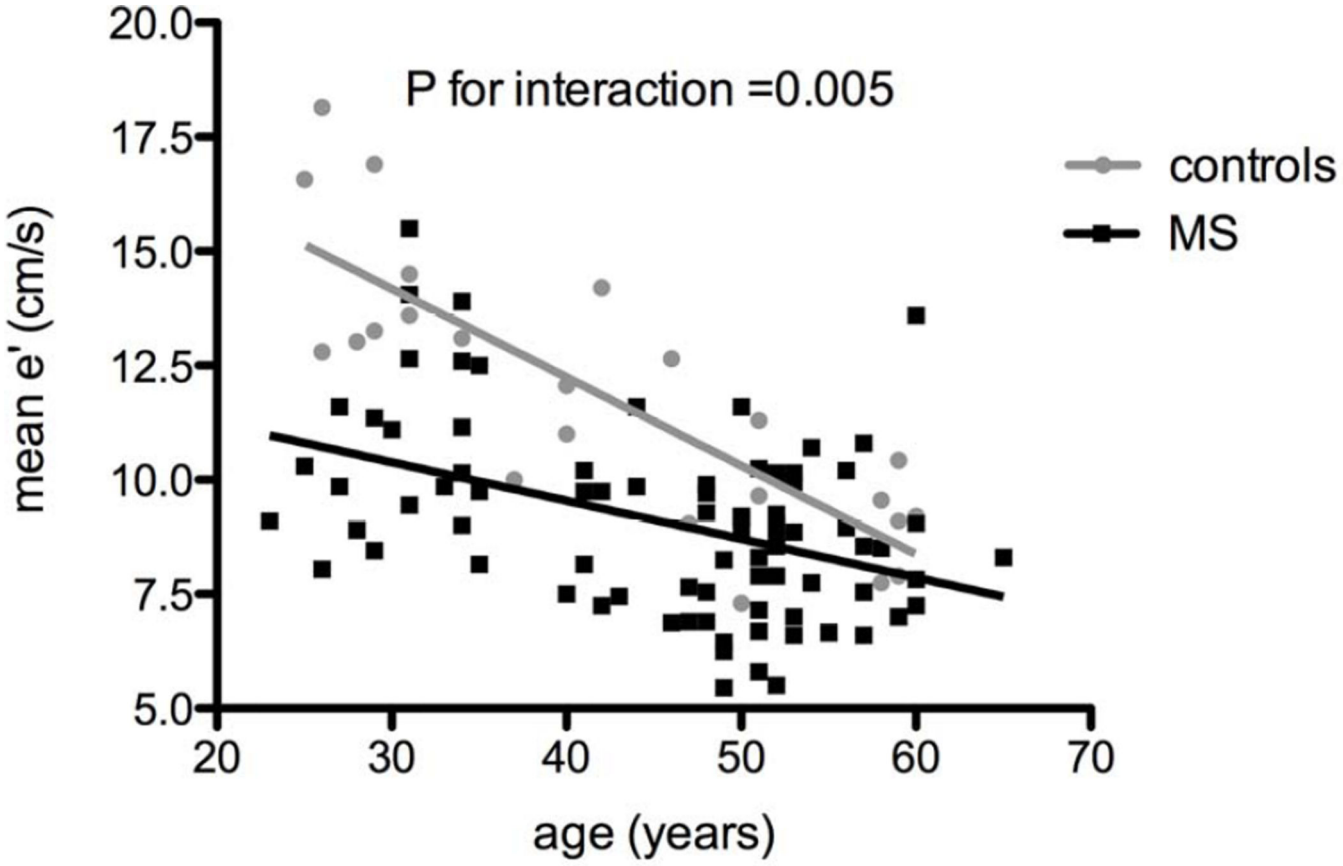

Figure 1. The effect of age on mean e' among subjects with and without MS

Individuals with MS had lower mean e' compared with those without MS, and this difference was more pronounced at younger ages (P for interaction=0.005). Black squares represent subjects with metabolic syndrome, and gray circles represent controls.

Table 1

Baseline characteristics by metabolic syndrome status

Variable	MS (n=90)	Controls (n=26)
Age (years)	46 ±10	43 ±12
Women	70 (78%)	17 (65%)
White	45 (50%)*	21 (81%)
Systolic blood pressure (mm Hg)	126 (16)*	109 (12)
Diastolic blood pressure (mm Hg)	79 (11)*	70 (7)
Body-mass index (kg/m^2)	39 (7)*	24 (3)
Triglyceride (mg/dl)	186 (120)*	86 (30)
High-density lipoprotein cholesterol (mg/dl)	43 (11)*	57 (12)
Smoker	11 (12%)*	0
Diabetes mellitus	35 (39%)*	0
Anti-hypertensive medication use	66 (73%)*	0
Severe hypertension	37 (32%)*	0
Elevated waist circumference	85 (94%)*	0
Elevated fasting triglyceride	57 (63%)*	0
Low HDL cholesterol	70 (78%)*	0
High blood pressure	80 (89%)*	0
Impaired fasting glucose	47 (52%)*	0
Three MS risk factors	39 (43%)*	0
Four MS risk factors	35 (39%)*	0
Five MS risk factors	16 (18%)*	0

Values are means (standard deviation) unless otherwise noted,

* P<0.05 for between group comparisons

Table 2

Echocardiographic measurements by metabolic syndrome status

Variable	MS (n=90)	Controls (n=26)	P-value
Dimension			
Left atrial dimension (mm)	37 (4)	32 (4)	<0.001
Left ventricular end diastolic dimension (mm)	46 (5)	47 (4)	0.25
Left ventricular end systolic dimension (mm)	30 (4)	31 (4)	0.46
Posterior wall thickness (mm)	9.9 (1.5)	7.8 (1.0)	<0.001
Interventricular septal thickness (mm)	10.0 (1.5)	7.7 (1.1)	<0.001
Relative wall thickness (cm)	0.44 (0.08)	0.33 (0.07)	<0.001
Left ventricular mass/height$^{2.7}$ (g/m$^{2.7}$)	39.9 (9.4)	28.8 (4.8)	<0.001
Left ventricular ejection fraction (%)	63 (5)	63 (4)	0.85
Diastolic parameters			
E (cm/s)	80 (16)	74 (15)	0.14
A (cm/s)	72 (17)	48 (13)	<0.001
E/A ratio	1.1 (0.3)	1.6 (0.5)	<0.001
Deceleration time (ms)	203 (44)	202 (34)	0.95
Mean e' (cm/s)	9.0 (2.0)	11.7 (3.0)	<0.001
E/mean e'	9.2 (2.4)	6.6 (1.7)	<0.001

Values are means (standard deviation)

Table 3

The association of metabolic syndrome with echocardiographic measures

	Age- and sex-adjusted		Age-, sex-, blood pressure- and BMI-adjusted		Age-, sex-, blood pressure-, BMI, and LV mass- adjusted	
	β estimate (s.e.)	P value	β estimate (s.e.)	P value	β estimate (s.e.)	P value
Left atrial dimension	5.0 (0.8)	<0.001	3.5 (1.4)	0.01	3.5 (1.4)	0.01
Left ventricular end diastolic dimension	−0.6 (1.1)	0.55				
Left ventricular end systolic dimension	−0.1 (0.9)	0.89				
Posterior wall thickness	2.2 (0.3)	<0.001	0.8 (0.5)	0.11		
Interventricular septal thickness	2.5 (0.3)	<0.001	1.1 (0.5)	0.02	1.2 (0.4)	0.001
Relative wall thickness	0.10 (0.02)	<0.001	0.07 (0.03)	0.01	0.07 (0.03)	0.01
Left ventricular mass/height$^{2.7}$	11.2 (2.0)	<0.001	−1.2 (2.8)	0.66		
Left ventricular ejection fraction (%)	−0.1 (1.2)	0.90				
E (cm/s)	6.4 (3.6)	0.08	−1.9 (5.6)	0.73		
A (cm/s)	21.0 (3.3)	<0.001	12.1 (5.2)	0.02	11.9 (5.2)	0.02
E/A ratio	−0.4 (0.1)	<0.001	−0.4 (0.1)	0.002	−0.4 (0.1)	0.002
Deceleration time (ms)	−3.3 (10.2)	0.75				
Mean e' (cm/s)	−2.2 (0.4)	<0.001	−1.7 (0.7)	0.015	−1.8 (0.7)	0.01
E/mean e‘	2.2 (0.5)	<0.001	0.8 (0.8)	0.32		

β estimate represents the change in echocardiographic measure in the presence versus absence of metabolic syndrome.