Preclinical Left Ventricular Diastolic Dysfunction in Metabolic Syndrome

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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 gender-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, antihypertensive 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′ ($p \leq 0.01$ 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 through 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. **(Am J Cardiol 2014;114:838−842)**

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 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 were 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 because of 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 mm Hg) or antihypertensive therapy, (d) decreased high-density lipoprotein cholesterol (<40 mg/dl in men or <50 mg/dl in women), and (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, left ventricular ejection fraction [LVEF] <50%, coronary artery disease, or valvular heart disease) were excluded from the study.

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See page 842 for disclosure information.

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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).

All participants underwent a comprehensive medical history and physical examination. Heart rate at rest, anthropometrics, blood pressure (obtained after 10 minutes 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 mm Hg, diastolic blood pressure ≥90 mm Hg, and/or current antihypertensive therapy. Severe hypertension was defined as taking 2 or more antihypertensive 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 before study enrollment.

Transthoracic echocardiography was performed with 1 to 5 MHz transducer and commercial ultrasound system (Philips iE33, Andover, MA) by an experienced sonographer. Studies were analyzed off-line using a digital echo interface (Philips XCelera, Andover, MA) 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 was calculated as the mean of the end-diastolic posterior and septal wall 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 was defined as LV mass index >44 g/m$^{2.7}$ in women and >48 g/m$^{2.7}$ in men.[8,9] Pulse-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.[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 3 consecutive cardiac cycles (when available). Repeated measurements of 10 scans showed an intra-observer coefficient of variation of 0.9% to 4.7% and an intraclass correlation coefficient of 91% to 99% for linear measurements.

Baseline clinical characteristics and echocardiographic measurements were summarized for participants with and without MS. Between-group differences in baseline measurements were assessed using 2-sample *t* tests or Pearson's chi-square tests as appropriate. The association of MS and measurements of cardiac structure and function was assessed using multivariable linear regression. Hierarchical models were constructed, first adjusting for age and gender and then further adjusting for systolic blood pressure, the use of antihypertensive medications, and body mass index (BMI). Lastly, analyses examining measurements 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 patients with MS using 1-way analysis of variance. We also examined the association of different components of MS and measurements of cardiac structure and function in participants with MS. Stepwise