European Heart Journal (2007) **28**, 553–559
doi:10.1093/eurheartj/ehl526

Clinical research
Heart failure/cardiomyopathy

Metabolic syndrome is associated with abnormal left ventricular diastolic function independent of left ventricular mass

Lisa de las Fuentes[1,2]*, Angela L. Brown[1,2], Santhosh J. Mathews[1,2], Alan D. Waggoner[1,2], Pablo F. Soto[2,3], Robert J. Gropler[2,3], and Víctor G. Dávila-Román[1,2]

[1]*Cardiovascular Imaging and Clinical Research Core Laboratory, Campus Box 8086, Washington University School of Medicine, 660 South Euclid Avenue, St Louis, MO 63110, USA;* [2]*Cardiovascular Division, Campus Box 8086, Washington University School of Medicine, 660 South Euclid Avenue, St Louis, MO 63110, USA; and* [3]*Cardiovascular Imaging Laboratory, Mallinckrodt Institute of Radiology, Campus Box 8067, Washington University School of Medicine, 660 South Euclid Avenue, St Louis, MO 63110, USA*

Received 14 September 2006; revised 8 December 2006; accepted 18 January 2007; online publish-ahead-of-print 20 February 2007

KEYWORDS
Metabolic syndrome;
Echocardiography;
Diastolic function;
Tissue doppler imaging;
Hypertension;
Obesity

Aim To characterize the extent to which metabolic syndrome criteria predict left ventricular (LV) structure and function.
Methods and results Metabolic syndrome criteria were assessed in 607 adults with normal LV function. The cohort was grouped according to the number of criteria satisfied: (1) Absent (0 criteria, $n = 110$); (2) Pre-Metabolic Syndrome (1–2 criteria, $n = 311$); and (3) Metabolic Syndrome ($\geq$3 criteria, $n = 186$). Echocardiography was used to assess LV structure (LV mass) and systolic (LVEF, Vs) and diastolic function, by pulse-wave Doppler (E/A ratio) and tissue Doppler imaging (Ve). LV volumes and LVEF were similar between groups. However, LV mass increased significantly and progressively ($LVM/Ht^{2.7}$, in $g/m^{2.7}$: 34.9 ± 6.7, 41.0 ± 9.5, 46.3 ± 11.0, $P < 0.001$); LV relaxation decreased progressively ($Ve_{global'}$, in cm/s: 13.5 ± 2.8, 12.1 ± 3.0, 10.5 ± 2.2, $P < 0.001$) from Absent to Pre-Metabolic Syndrome to Metabolic Syndrome groups, respectively. Multiple variable analyses showed that diastolic blood pressure, waist circumference, and triglyceride levels were independent predictors of Ve after adjustment for LV mass.
Conclusion Patients with metabolic syndrome have LV diastolic dysfunction independent of LV mass. These functional abnormalities may partially explain the increased cardiovascular morbidity and mortality associated with metabolic syndrome.

Introduction

The metabolic syndrome represents a clustering of cardiovascular risk factors affecting ~22% of the adult population in industrialized countries and over 40% of the those aged 50 and older.[1,2] These risk factors have been shown to act synergistically, via mechanisms poorly defined, to increase the risk of adverse cardiovascular events including coronary artery disease (CAD) and congestive heart failure, and are associated with high cardiovascular morbidity and mortality.[2–4] Although studies have shown that hypertension, diabetes mellitus, and obesity adversely affect cardiac structure and function, the extent to which individual and clustering components of the metabolic syndrome predict subclinical left ventricular (LV) systolic and/or diastolic dysfunction has not been well characterized.[5–9]

LV hypertrophy (LVH) imparts increased risk of cardiovascular morbidity and mortality, including development of systolic and diastolic dysfunction, and progression to heart failure.[10–12] Although the progressive addition of metabolic syndrome risk factors, such as obesity, diabetes, and/or dyslipidaemia, is associated with increased LV mass, independent of hypertension, the effects of the metabolic syndrome and of each of its component criteria on cardiac structure and function has not been well characterized.[13] Thus, the purpose of this study was to evaluate the effects of the metabolic syndrome and the individual components of the syndrome on echocardiographically-determined LV structure and function.

Methods

Study population

The study cohort consisted of 607 subjects (out of 872 consecutive, ambulatory subjects), aged 21 and older meeting study criteria. All study subjects underwent a complete cardiovascular evaluation after an 8 h fast, including: (1) history and physical examination; (2) heart rate, blood pressure (obtained after 10 min of rest in the

* Corresponding author. Tel: +1 314 362 1076; fax: +314 747 8170.
E-mail address: lfuentes@wustl.edu

sitting position, expressed as the average of three consecutive measurements in each arm); (3) fasting serum glucose and insulin (for those not receiving insulin and/or oral hypoglycemic agents); (4) fasting plasma lipids [i.e. triglyceride, high-density lipoprotein cholesterol (HDL-C), total cholesterol, and low-density lipoprotein cholesterol (LDL-C) concentrations]; and (5) comprehensive two-dimensional and Doppler echocardiogram. The Human Research Protection Office at Washington University approved of this protocol; informed consent was obtained prior to study enrolment.

Metabolic syndrome was diagnosed according to the amended National Cholesterol Education Program's Adult Treatment Panel III (ATP-III) guidelines in individuals meeting three or more of the following criteria: (a) increased waist circumference (>102 cm in men or >88 cm in women); (b) increased fasting triglyceride (>1.7 mmol/L); (c) high blood pressure (≥130/≥85 mmHg) or antihypertensive therapy; (d) decreased HDL-C (<0.45 mmol/L in men or <0.56 mmol/L in women); (e) impaired fasting glucose (≥5.6 mmol/L).[14,15] Those receiving niacin and/or fibric acid derivatives were considered to have met the criteria for both increased serum triglyceride and decreased HDL-C.[14,15]

Systemic hypertension was defined according to Joint National Committee VII (JNC VII) criteria, as a BP ≥140/≥90 mmHg and/or current antihypertensive therapy.[16] Overweight and obesity were defined as a body mass index between 25–30 kg/m^2 and >30 kg/m^2, respectively. LDL-C was calculated according to Friedewald's equation when TG was ≤5.7 mmol/L; otherwise it was directly measured by ultracentrifugation.[17] Diabetes was defined according to revised American Diabetes Association criteria, as (a) fasting serum glucose level ≥7.0 mmol/L and/or (b) current medical therapy with an oral hypoglycaemic agent and/or insulin.[18] CAD was defined as (a) history and/or treatment for angina and/or myocardial infarction; (b) history of coronary artery revascularization procedures and/or coronary angiography with >50% stenosis in one or more of the major coronary arteries; and/or (c) regional wall motion abnormalities on rest echocardiography.

Exclusion criteria included the following: (1) history or findings of cardiovascular disease including heart failure symptoms or systolic dysfunction (LVEF <55%), coronary artery disease, significant valvular heart disease (i.e. greater than mild valvular insufficiency or stenosis), and/or hypertrophic cardiomyopathy; (2) pregnancy or lactating; and/or (3) major systemic illness.

Echocardiography

Echocardiography was performed in harmonic imaging mode by use of a 3.5-MHz transducer and commercial ultrasound system (Sequoia-C256, Acuson-Siemens, Mountain View, CA). Internal dimensions, left ventricle wall thickness, and LVEF (by modified Simpson's rule) were measured according to published recommendations.[19] Left atrial diameter was measured in the parasternal long-axis view. The relative wall thickness (RWT) was calculated as follows: LV end-diastolic diameter / 2 • end-diastolic posterior wall thickness. The LV mass was determined by the M-mode-derived cubed method and indexed to height$^{2.7}$ (LVM/Ht$^{2.7}$) to correct for body habitus; LVH was defined as LVM/Ht$^{2.7}$ ≥51 g/m$^{2.7}$ for men and ≥49.5 g/m$^{2.7}$ for women.[20]

Pulsed-wave Doppler (PWD)-derived transmitral inflow velocities were obtained in the apical 4-chamber view with the sample volume placed at the mitral valve leaflet tips.[21] Measurements included the transmitral early diastolic (E-wave) and atrial (A-wave) velocities to calculate E/A ratio, E-wave deceleration time, and the isovolumic relaxation time.[21] Tissue Doppler imaging (TDI) was used to obtain LV myocardial velocities in the apical 4- and 2-chamber views with a 2 mm sample volume placed at the lateral, septal, anterior, and inferior mitral annulus.[8,21–25] Measurements included the systolic (Vs) and early diastolic (Ve) myocardial velocities. Values reported include the velocities at the septum (Vs_{septal} and Ve_{septal}) and the average of the four annular sites (Vs_{global} and Ve_{global}). LV diastolic dysfunction was defined as follows: (1) PWD criteria: E/A ratio <1 if age <55 or <0.8 if age ≥55, and/or DT >240 ms; (2) TDI criteria: Ve_{global} ≤12.9 cm/s if age <40; Ve_{global} ≤10.2 cm/s age 40–59; and Ve_{global} ≤7.2 cm/s if age ≥60.[26] All echocardiographic measurements were averaged over three consecutive cardiac cycles, measured by a single investigator blinded to all other variables.

Statistical analysis

Statistics were performed using SAS software (Version 9.1, SAS Institute, Cary, NC). For analysis, the study cohort was grouped according to the number of metabolic syndrome criteria satisfied: Absent (0 criteria), Pre-Metabolic Syndrome (1–2 criteria), and Metabolic Syndrome (≥3 criteria). All *P*-values for comparisons of variables presented in *Tables 1* and *2* were adjusted for multiple comparisons using a Bonferroni adjustment. Values for continuous data were presented as the mean ± SD. Group differences were assessed by analysis of variance and the Dunnett *post-hoc* test for multiple comparisons. The Cochran–Armitage trend test was used to test group trends for categorical variables. The odds ratios and 95% confidence intervals (CI) were calculated for Pre-Metabolic - Syndrome and Metabolic Syndrome being associated with PWD- and TDI-determined LV diastolic dysfunction. Stepwise multiple variable regression models determined the variables most predictive of Vs_{global}, Ve_{global}, and E/A ratio and included: age, LVM/Ht$^{2.7}$, Vs_{global} (except when Vs_{global} was the dependent variable), metabolic syndrome group assignment, and the individual metabolic syndrome criteria expressed as continuous variables (i.e. waist circumference, triglyceride, HDL-C, systolic and diastolic blood pressures, and fasting glucose).

The models were re-analyzed substituting the continuous variable glucose with its dichotomous counterpart (i.e. impaired fasting glucose) to include diabetics in the models. Variables that were not normally distributed were log- or reciprocally-transformed for analysis. Variable entry into the stepwise regression models required a *P*-value < 0.10; a *P*-value < 0.05 was considered statistically significant.

Results

Characteristics of study population

Demographic and clinical characteristics of the 607 subjects (mean age: 49 ± 13, 59% female) were grouped according to the number of metabolic syndrome criteria (*Table 1*). Gender and racial distributions were similar among the three groups. Despite not meeting waist circumference criteria for visceral obesity, 47% in the Absent group were either overweight or obese. Hypertension was the most prevalent criteria in the Pre-Metabolic Syndrome group, while hypertension, increased waist circumference, and hypertriglyceridaemia were the three most common criteria present in the Metabolic Syndrome group (*Figure 1*).

LV structure and systolic function

The LV dimensions, volumes, and LVEF were similar across the three groups (*Table 2*). The RWT, LVM/Ht$^{2.7}$, and left atrial diameter exhibited stepwise increases from the Absent to Pre-Metabolic Syndrome to Metabolic Syndrome groups. LVH was present in 2% of the Absent, 14% of the Pre-Metabolic Syndrome, and 31% of the Metabolic Syndrome groups ($P < 0.0001$). Although the LVEF was similar among the three groups, the TDI-derived Vs_{septal}, but not Vs_{global}, (measures of longitudinal systolic myocardial contractility) was significantly lower in the Metabolic Syndrome group compared with the Absent group ($P = 0.006$). Univariate

Table 1 Characteristics of the study population

	Absent ($n = 110$)[a]	Pre-MetS ($n = 311$)[a]	MetS ($n = 186$)[a]	*P*-values		
				Adjusted Omnibus[b]	Pre-MetS vs. Absent[c]	MetS vs. Absent[c]
Age, years	44 ± 12	48 ± 13	51 ± 11	0.0004	0.003	<0.0001
Female, *n* (%)	64 (58)	184 (59)	108 (58)			
African American, *n* (%)	21 (19)	70 (23)	47 (25)			
Body mass index, kg/m^2	25 ± 3	29 ± 6	35 ± 6	<0.0001	<0.0001	<0.0001
Waist circumference, cm	79 ± 10	91 ± 15	104 ± 13	<0.0001	<0.0001	<0.0001
Systolic BP, mmHg	110 ± 9	124 ± 17	131 ± 15	<0.0001	<0.0001	<0.0001
Diastolic BP, mmHg	73 ± 6	80 ± 9	83 ± 8	<0.0001	<0.0001	<0.0001
HDL cholesterol, mmol/L	1.6 ± 0.4	1.5 ± 0.4	1.9 ± 0.3	<0.0001	0.0002	<0.0001
Triglyceride, mmol/L	0.9 ± 0.3	1.3 ± 0.6	2.2 ± 1.3	<0.0001	0.0002	<0.0001
Glucose, mmol/L[a]	4.6 ± 0.5	4.9 ± 0.8	5.6 ± 1.3	<0.0001	0.02	<0.0001
Total cholesterol, mmol/L	5.0 ± 0.8	5.0 ± 1.0	5.0 ± 1.0			
LDL cholesterol, mmol/L	2.9 ± 0.8	3.0 ± 0.8	2.9 ± 0.9			
Heart rate, bpm	63 ± 11	64 ± 10	69 ± 11	<0.0001		<0.0001
Insulin, μU/mL[a]	6.3 ± 4.0	9.3 ± 8.1	18.0 ± 16.2	<0.0001	<0.0001	<0.0001
Past medical history, %						
Hypertension	—	154 (50)	129 (69)	<0.0001		
Type 2 diabetes mellitus	—	20 (7)	73 (41)	<0.0001		
Current smoker	7 (6)	33 (11)	18 (10)			
Prior smoker	25 (23)	96 (31)	65 (35)			
Medical therapy, %						
Anti-hypertensive	—	119 (38)	104 (56)	<0.0001		
Statin	1 (1)	36 (12)	49 (26)	<0.0001		
Fibrate	—	1 (0)	8 (4)	0.03		
Niacin	—	—	6 (3)			
Oral hypoglycaemic	—	9 (3)	54 (29)	<0.0001		
Insulin	—	2 (1)	5 (3)			

Italicized variables represent metabolic syndrome criteria.
[a]Glucose and insulin only obtained in fasting subjects not taking oral hypoglycaemic agents or insulin (Absent: $n = 111$, Pre-MetS: $n = 297$, MetS: $n = 127$).
[b]The omnibus *P*-value for continuous variables and the Cochran-Armitage trend test for categorical variables are adjusted per Bonferroni.
[c]Pair-wise comparisons of categorical variables by Dunnett.

analyses showed that systolic and diastolic blood pressure, glucose (only for Vs_{global}), triglyceride, age, and LVM/Ht$^{2.7}$ were significant predictors of Vs_{septal} and Vs_{global}; however, stepwise multiple variable analysis found that only age and LVM/Ht$^{2.7}$ were independent predictors of Vs_{septal} (model $r^2 = 0.16$), and that age, systolic and diastolic blood pressures were independent predictors of Vs_{global} (model $r^2 = 0.22$).

LV diastolic function in Pre-Metabolic Syndrome and Metabolic Syndrome

The E/A ratio exhibited a stepwise decrease from the Absent to the Pre-Metabolic Syndrome to the Metabolic Syndrome groups, primarily a result of increased A-wave velocity; the deceleration time and isovolumic relaxation time were significantly longer in the Metabolic Syndrome group (*Table 2*). The TDI-derived Ve_{septal} and Ve_{global} were significantly lower in both the Metabolic Syndrome and Pre-Metabolic Syndrome than in the Absent group ($P \leq 0.0002$ for all). These findings suggest that there is a progressive impairment in LV relaxation as the number of Metabolic Syndrome criteria increase.

The prevalence of LV diastolic dysfunction by PWD- and TDI-derived indices ranged from 7–9% in the Absent group to 17–18% in the Pre-Metabolic Syndrome group and 29–35% in the Metabolic Syndrome group (*Figure 2*). In the Pre-Metabolic Syndrome group, the odds ratio for detecting LV diastolic dysfunction were 2.6 (95% CI: 1.2–5.6, $P = 0.01$) by PWD and 2.2 (95% CI: 1.1–4.5, $P = 0.03$) by TDI; in the Metabolic Syndrome group the odds ratio were 5.2 (95% CI: 2.4–11.4, $P < 0.0001$), and 5.5 (95% CI: 2.7–11.3, $P < 0.0001$), respectively.

Multiple variable regression models of LV diastolic function

To determine the contribution of each component of the metabolic syndrome to measures of LV relaxation (i.e. Ve_{global} velocity and E/A ratio), univariate and stepwise multiple variable regression models were developed to include systolic and diastolic blood pressures, waist circumference, glucose, HDL-C, triglyceride, and metabolic syndrome group assignment (Absent, Pre-Metabolic Syndrome, or Metabolic Syndrome) with covariates including age, LVM/Ht$^{2.7}$, and Vs_{global} (*Table 3*). The univariate analyses demonstrated that all variables were significantly associated with Em_{global} ($P < 0.0001$ for all) except HDL-C. Stepwise multiple variable regression analyses demonstrated that age, Vs_{global}, diastolic blood pressure, waist circumference, LVM/Ht$^{2.7}$, and triglyceride remained independently associated with Ve_{global} ($r^2 = 0.75$). The univariate analyses for E/A ratio (*Table 3*) showed that all of the variables except HDL-C had significant associations with the E/A ratio ($p \leq 0.0004$

Table 2 Echocardiographic parameters of LV structure and function

	Absent ($n = 110$)	Pre-MetS ($n = 311$)	MetS ($n = 186$)	*P*-values		
				Adjusted Omnibus[a]	Pre-MetS vs. Absent[b]	MetS vs. Absent[b]
LV structure						
LVEDD, mm	48 ± 4	49 ± 5	49 ± 5			
LVESD, mm	32 ± 4	31 ± 5	32 ± 5			
LVEDV, ml	90 ± 23	91 ± 23	92 ± 22			
LVESV, ml	33 ± 10	32 ± 11	33 ± 11			
RWT	0.37 ± 0.05	0.40 ± 0.06	0.43 ± 0.08	<0.0001	0.0007	<0.0001
LVM/Ht$^{2.7}$, g/m$^{2.7}$	34.9 ± 6.7	41.0 ± 9.5	46.3 ± 11.0	<0.0001	<0.0001	<0.0001
LA diameter, mm	36 ± 5	38 ± 5	40 ± 6	<0.0001	0.0001	<0.0001
LV systolic function						
LVEF, %	64 ± 4	65 ± 6	65 ± 5			
Vs_{septal}, cm/s	8.2 ± 1.1	8.0 ± 1.2	7.7 ± 0.9	0.04		0.0006
Vs_{global}, cm/s	8.3 ± 1.0	8.2 ± 1.1	8.0 ± 0.8			
LV diastolic function						
E-wave, cm/s	72 ± 14	72 ± 16	74 ± 17			
A-wave, cm/s	48 ± 14	55 ± 15	66 ± 18	<0.0001	<0.0001	<0.0001
E/A ratio	1.6 ± 0.5	1.4 ± 0.5	1.2 ± 0.5	<0.0001	<0.0001	<0.0001
DT, ms	198 ± 33	202 ± 34	216 ± 40	0.0002		<0.0001
IVRT, ms	88 ± 15	95 ± 19	95 ± 19	0.05	0.001	0.002
Ve_{septal}, cm/s	11.5 ± 2.4	10.4 ± 2.7	9.0 ± 2.1	<0.0001	0.0002	<0.0001
Ve_{global}, cm/s	13.5 ± 2.8	12.1 ± 3.0	10.5 ± 2.2	<0.0001	<0.0001	<0.0001

[a]The omnibus *P*-values are adjusted per Bonferroni.
[b]Pair-wise comparisons of categorical variables by Dunnett.
LA, left atrial; LVEDD, LV end-diastolic diameter; LVEDV, LV end-diastolic volume; LVESD, LV end-systolic diameter; LVESV, LV end-systolic volume.

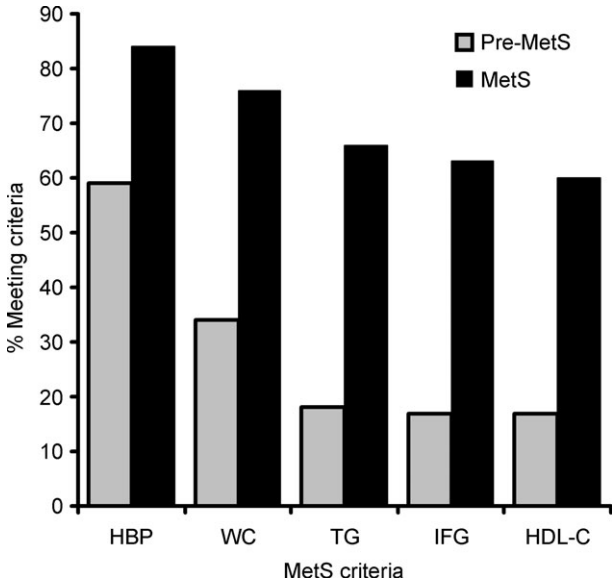

Figure 1 Prevalence of individual criteria in the Pre-Metabolic Syndrome and Metabolic Syndrome groups. MetS: Metabolic Syndrome.

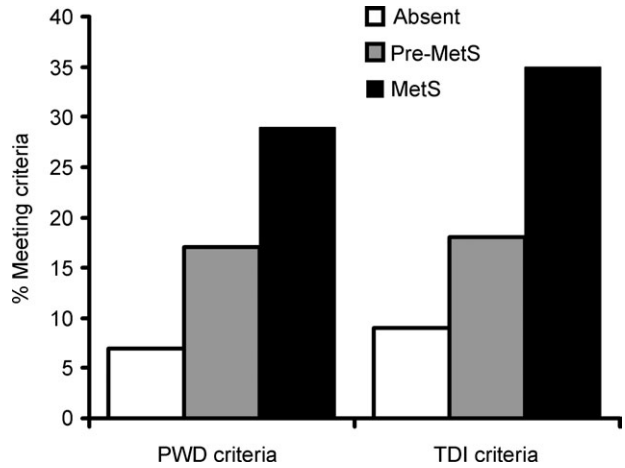

Figure 2 Prevalence of diastolic dysfunction by pulse-wave Doppler and tissue Doppler imaging criteria.

for all). Stepwise multiple variable regression analyses showed that age, diastolic blood pressure, Vs_{global}, systolic blood pressure, and HDL-C were independently associated with E/A ratio (model $r^2 = 0.50$). Importantly, metabolic syndrome group assignment was not independently associated with Ve_{global} or E/A ratio in the multiple variable analyses.

The regression models used fasting glucose level as a continuous variable; these were not obtained in diabetic subjects receiving oral hypoglycaemic or insulin therapy ($n = 72$), which may result in the exclusion of more severe metabolic phenotypes from analysis. As such, the regression models may have underestimated the contribution of impaired fasting glucose to measures of LV diastolic function. Re-analysis of the stepwise multiple variable regression models (data not shown) including the presence or absence of impaired fasting glucose (as a dichotomous variable) instead of fasting glucose resulted in models where the metabolic syndrome group variable was retained for both

Table 3 Univariate and stepwise multiple variable analyses of Em and E/A ratio for each component of the metabolic syndrome and covariates

Variable	Ve_{global}, cm/s			E/A Ratio		
	Univariate		Multiple variable	Univariate		Multiple variable
	r	*P*-value	*P*-value	*r*	*P*-value	*P*-value
Systolic BP	0.20	<0.0001		0.13	<0.0001	0.005
Diastolic BP	0.14	<0.0001	<0.0001	0.09	<0.0001	<0.0001
Triglyceride	0.04	<0.0001	0.01	0.03	<0.0001	
Glucose	0.04	<0.0001		0.02	0.0004	
Waist circumference	0.05	<0.0001	<0.0001	0.03	<0.0001	
HDL-C						0.02
MetS group	0.12	<0.0001		0.08	<0.0001	
Age	0.54	<0.0001	<0.0001	0.43	<0.0001	<0.0001
$LVM/Ht^{2.7}$	0.11	<0.0001	0.005	0.04	<0.0001	
Vs_{global}	0.42	<0.0001	<0.0001	0.18	<0.0001	<0.0001
Model r^2			0.75			0.50

BP, Blood pressure. Blank fields not significant.

Ve_{global} ($P \leq 0.0001$, model $r^2 = 0.74$) and E/A ($P = 0.0009$, model $r^2 = 0.50$); impaired fasting glucose was not retained in either model.

Subgroup analyses in non-hypertensive and normal waist circumference cohorts

To determine whether metabolic syndrome variables remained predictive of Ve_{global} in a subgroup that did not meet the JNC VII diagnostic criteria for systemic hypertension or for the ATP-III criteria for increased waist circumference, the regression analyses were repeated. In the subgroup without systemic hypertension (i.e. BP <140/<90 mmHg; Absent group: $n = 110$, Pre-Metabolic Syndrome group: $n = 157$, Metabolic Syndrome group: $n = 57$), $LVM/Ht^{2.7}$ was significantly greater in the Pre-Metabolic Syndrome and Metabolic Syndrome groups compared with the Absent group ($P < 0.0001$ for both). The multiple variable regression models were also largely unchanged except that triglyceride was not an independent predictor of Ve (data not shown).

Similar analyses in those who did not meet the ATP-III criteria for increased waist circumference (i.e. ≤102 cm in men and ≤88 cm in women; Absent: $n = 110$, Pre-Metabolic Syndrome: $n = 190$, Metabolic Syndrome: $n = 34$) showed that both $LVM/Ht^{2.7}$ and RWT were significantly greater and Ve_{septal} and Ve_{global} were significantly lower in the Pre-Metabolic Syndrome and Metabolic Syndrome groups compared with the Absent group ($P \leq 0.002$ for all). However, waist circumference was no longer an independent predictor of Ve_{global}.

Discussion

This study evaluated echocardiographically derived measurements of LV structure and function in a cross-sectional cohort of subjects who were grouped according to the number of metabolic syndrome criteria met. Although LV volumes and LVEF were similar among the three groups, RWT and $LVM/Ht^{2.7}$ and the prevalence of diastolic dysfunction increased progressively from the Absent to the Pre-Metabolic Syndrome and Metabolic Syndrome groups. Of note, the Absent group, while not meeting any criteria for metabolic syndrome, did not represent a 'normal control' group since 47% were either overweight or obese. This study revealed that while each of the variables contributing to metabolic syndrome was correlated with LV relaxation (i.e. Ve_{global}) in univariate analyses (HDL-C excluded), only diastolic blood pressure, waist circumference, and triglyceride remained independently associated with Ve_{global} in models that also included age and LV mass.

Metabolic syndrome and diastolic dysfunction

Results of the present study are consistent with those of prior studies that identified hypertension and obesity as independent predictors of impaired LV diastolic function.[8,13,27] However, few studies have evaluated the relationship between metabolic syndrome and echocardiographically derived measures of LV structure and function.[5,28,29] In the present study, measurements of diastolic (Ve) function worsened progressively from the Absent to the Pre-Metabolic Syndrome and Metabolic Syndrome groups, indicating impairment in diastolic function with increasing burden of metabolic syndrome.

Increased LV mass, RWT, and deceleration time have been reported in hypertensive subjects with metabolic syndrome compared with a hypertensive cohort without the syndrome.[28] In the Strong Heart Study, those with metabolic syndrome had greater LV mass and RWT and significantly lower E/A ratio; however, LV diastolic function was not characterized in Pre-Metabolic Syndrome.[5] The present study, by use of improved measures to detect LV relaxation (i.e. Ve), identifies a Pre-Metabolic Syndrome group with impaired LV diastolic function. Furthermore, the present study demonstrated that in a subgroup of subjects without systemic hypertension (as defined by JNC VII), LV mass was significantly greater and Ve significantly lower in the Metabolic Syndrome group; both systolic and diastolic blood pressures remained independent predictors of LV relaxation in this subgroup. Thus, even blood pressure levels within the

non-hypertensive range may contribute to the development of subclinical LV diastolic dysfunction.

Progressive abnormalities in LV mass and diastolic dysfunction

Although LV mass exhibited a direct correlation with measures of impaired relaxation (both Ve_{global} and E/A ratio) in univariate analyses, its predictive value was relatively weak for Ve_{global}, selected after age, Vs_{global}, diastolic blood pressure, waist circumference, and triglyceride. Hypertension is an established risk factor for increased LV mass; the current study suggests that LVH may represent an intermediate phenotype, and that specific components of metabolic syndrome (i.e. blood pressure and waist circumference) may carry higher risk for the development of LV diastolic dysfunction. However, the mechanisms by which hypertension and visceral obesity lead to impaired LV diastolic function remain to be defined. Our group and others have previously shown that visceral obesity is associated with diastolic dysfunction, an effect that may be mediated by an obesity-related pro-inflammatory state and/or by suppression of adiponectin expression.[8,30–32] Other potential mechanisms whereby metabolic syndrome contribute to impaired LV diastolic function include endothelial dysfunction, abnormalities in myocardial perfusion and/or metabolic substrate utilization, inflammation and oxidative stress, interstitial fibrosis, impaired ventricular–vascular interaction, and others.[33–42]

Limitations

The cross-sectional design of this study precludes outcome analyses. Ambulatory blood pressure measurements, which have been shown to be more predictive of hypertensive end-organ damage, are not available in this study. Although regression models identified high blood pressure and abdominal obesity as the major contributors to LV structure and function, this may apply only to the adult population in the United States where obesity and impaired glucose tolerance/insulin resistance frequently coexist. Furthermore, insulin resistance may have been found to have a more significant association with LV structure and function if metabolic syndrome was diagnosed according to the World Health Organization criteria. Although insulin and glucose were not obtained in diabetic subjects who were treated with insulin and/or oral hypoglycaemics, the impact of this limitation was minimized by performing regression analyses using impaired fasting glucose as criteria, which includes subjects with diabetes.

Conclusions

Individuals with the metabolic syndrome and normal LV systolic function frequently show abnormalities in LV diastolic function (i.e. impaired relaxation). These findings are also evident in subjects with only one or two metabolic syndrome criteria (or Pre-Metabolic Syndrome). Blood pressure and increased waist circumference are independently associated with LV diastolic function in models that also include LV mass. These functional abnormalities may partially explain the increased cardiovascular morbidity and mortality associated with metabolic syndrome.

Acknowledgements

Supported in part by grants from the National Institutes of Health [R01HL58878 (V.G.D.-R.), R01HL71782 (V.G.D.-R.), P01HL13581 (R.J.G.), P50HL083762 (V.G.D.-R.), R01AG15466 (R.J.G.), S10RR14778 (V.G.D.-R.), K24HL67002 (V.G.D.-R.), K12RR023249 (L.d.l.F.), K23HL077179 (P.F.S.), M01RR00036 (General Clinical Research Center to Washington University)] and from the Robert Wood Johnson (L.d.l.F., P.F.S.) and Barnes-Jewish Hospital Foundation (to the Cardiovascular Imaging and Clinical Research Core Laboratory) Foundations.

Conflict of interest: none declared.

References

1. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the Third National Health and Nutrition Examination Survey. *JAMA* 2002;**287**:356–359.
2. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, Salonen JT. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 2002;**288**:2709–2716.
3. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 1988;**37**:1595–1607.
4. Ninomiya JK, L'Italien G, Criqui MH, Whyte JL, Gamst A, Chen RS. Association of the metabolic syndrome with history of myocardial infarction and stroke in the Third National Health and Nutrition Examination Survey. *Circulation* 2004;**109**:42–46.
5. Chinali M, Devereux RB, Howard BV, Roman MJ, Bella JN, Liu JE, Resnick HE, Lee ET, Best LG, de Simone G. Comparison of cardiac structure and function in American Indians with and without the metabolic syndrome (the Strong Heart Study). *Am J Cardiol* 2004;**93**:40–44.
6. Rutter MK, Parise H, Benjamin EJ, Levy D, Larson MG, Meigs JB, Nesto RW, Wilson PW, Vasan RS. Impact of glucose intolerance and insulin resistance on cardiac structure and function: Sex-related differences in the Framingham Heart Study. *Circulation* 2003;**107**:448–454.
7. Liu JE, Palmieri V, Roman MJ, Bella JN, Fabsitz R, Howard BV, Welty TK, Lee ET, Devereux RB. The impact of diabetes on left ventricular filling pattern in normotensive and hypertensive adults: The Strong Heart Study. *J Am Coll Cardiol* 2001;**37**:1943–1949.
8. Peterson LR, Waggoner AD, Schechtman KB, Meyer T, Gropler RJ, Barzilai B, Davila-Roman VG. Alterations in left ventricular structure and function in young healthy obese women: Assessment by echocardiography and tissue Doppler imaging. *J Am Coll Cardiol* 2004;**43**:1399–1404.
9. Fang ZY, Najos-Valencia O, Leano R, Marwick TH. Patients with early diabetic heart disease demonstrate a normal myocardial response to dobutamine. *J Am Coll Cardiol* 2003;**42**:446–453.
10. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 1990;**322**:1561–1566.
11. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med* 1991;**114**:345–352.
12. Devereux RB, Koren MJ, de Simone G, Roman MJ, Laragh JH. Left ventricular mass as a measure of preclinical hypertensive disease. *Am J Hypertens* 1992;**5**:175S–181S.
13. de Simone G, Palmieri V, Bella JN, Celentano A, Hong Y, Oberman A, Kitzman DW, Hopkins PN, Arnett DK, Devereux RB. Association of left ventricular hypertrophy with metabolic risk factors: The HyperGEN study. *J Hypertens* 2002;**20**:323–331.
14. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F. Diagnosis and management of the metabolic syndrome: An American Heart Association/National Heart, Lung, and Blood Institute scientific statement: Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary. *Circulation* 2005;**112**:e285–e290.
15. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the third report of the National Cholesterol Education Program (NCEP) (Adult Treatment Panel III). *JAMA* 2001;**285**:2486–2497.
16. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ. Seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 2003;**42**:1206–1252.

17. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;**18**:499–502.
18. Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, Kitzmiller J, Knowler WC, Lebovitz H, Lernmark A, Nathan D, Palmer J, Rizza R, Saudek C, Shaw J, Steffes M, Stern M, Tuomilehto J, Zimmet P. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 2003;**26**: 3160–3167.
19. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography committee on standards, subcommittee on quantitation of two-dimensional echocardiograms. *J Am Soc Echocardiogr* 1989;**2**:358–367.
20. de Simone G, Daniels SR, Devereux RB, Meyer RA, Roman MJ, de Divitiis O, Alderman MH. Left ventricular mass and body size in normotensive children and adults: Assessment of allometric relations and impact of overweight. *J Am Coll Cardiol* 1992;**20**:1251–1260.
21. Quinones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Recommendations for quantification of Doppler echocardiography: A report from the Doppler quantification task force of the nomenclature and standards committee of the American Society of Echocardiography. *J Am Soc Echocardiogr* 2002;**15**:167–184.
22. de las Fuentes L, Waggoner AD, Brown AL, Davila-Roman VG. Plasma triglyceride level is an independent predictor of altered left ventricular relaxation. *J Am Soc Echocardiogr* 2005;**18**:1285–1291.
23. Choong CY, Herrmann HC, Weyman AE, Fifer MA. Preload dependence of Doppler-derived indexes of left ventricular diastolic function in humans. *J Am Coll Cardiol* 1987;**10**:800–808.
24. Wang M, Yip GW, Wang AY, Zhang Y, Ho PY, Tse MK, Lam PK, Sanderson JE. Peak early diastolic mitral annulus velocity by tissue Doppler imaging adds independent and incremental prognostic value. *J Am Coll Cardiol* 2003;**41**:820–826.
25. Dumesnil JG, Paulin C, Pibarot P, Coulombe D, Arsenault M. Mitral annulus velocities by Doppler tissue imaging: Practical implications with regard to preload alterations, sample position, and normal values. *J Am Soc Echocardiogr* 2002;**15**:1226–1231.
26. Alam M, Wardell J, Andersson E, Samad BA, Nordlander R. Characteristics of mitral and tricuspid annular velocities determined by pulsed wave Doppler tissue imaging in healthy subjects. *J Am Soc Echocardiogr* 1999; **12**:618–628.
27. Dwyer EM, Asif M, Ippolito T, Gillespie M. Role of hypertension, diabetes, obesity, and race in the development of symptomatic myocardial dysfunction in a predominantly minority population with normal coronary arteries. *Am Heart J* 2000;**139**:297–304.
28. Mule G, Nardi E, Cottone S, Cusimano P, Volpe V, Piazza G, Mongiovi R, Mezzatesta G, Andronico G, Cerasola G. Influence of metabolic syndrome on hypertension-related target organ damage. *J Intern Med* 2005;**257**: 503–513.
29. Wong CY, O'Moore-Sullivan T, Fang ZY, Haluska B, Leano R, Marwick TH. Myocardial and vascular dysfunction and exercise capacity in the metabolic syndrome. *Am J Cardiol* 2005;**96**:1686–1691.
30. Wong CY, O'Moore-Sullivan T, Leano R, Byrne N, Beller E, Marwick TH. Alterations of left ventricular myocardial characteristics associated with obesity. *Circulation* 2004;**110**:3081–3087.
31. Ouchi N, Kihara S, Arita Y, Maeda K, Kuriyama H, Okamoto Y, Hotta K, Nishida M, Takahashi M, Nakamura T, Yamashita S, Funahashi T, Matsuzawa Y. Novel modulator for endothelial adhesion molecules: Adipocyte-derived plasma protein adiponectin. *Circulation* 1999;**100**:2473–2476.
32. Kuwahara F, Kai H, Tokuda K, Takeya M, Takeshita A, Egashira K, Imaizumi T. Hypertensive myocardial fibrosis and diastolic dysfunction: Another model of inflammation? *Hypertension* 2004;**43**:739–745.
33. Ogata T, Miyauchi T, Sakai S, Takanashi M, Irukayama-Tomobe Y, Yamaguchi I. Myocardial fibrosis and diastolic dysfunction in deoxycorticosterone acetate-salt hypertensive rats is ameliorated by the peroxisome proliferator-activated receptor-alpha activator fenofibrate, partly by suppressing inflammatory responses associated with the nuclear factor-kappa-b pathway. *J Am Coll Cardiol* 2004;**43**:1481–1488.
34. Peterson LR, Herrero P, Schechtman KB, Racette SB, Waggoner AD, Kisrieva-Ware Z, Dence C, Klein S, Marsala J, Meyer T, Gropler RJ. Effect of obesity and insulin resistance on myocardial substrate metabolism and efficiency in young women. *Circulation* 2004;**109**:2191–2196.
35. Herrero P, Peterson LR, McGill JB, Matthew S, Lesniak D, Dence C, Gropler RJ. Increased myocardial fatty acid metabolism in patients with type 1 diabetes mellitus. *J Am Coll Cardiol* 2006;**47**:598–604.
36. Srinivasan M, Herrero P, McGill JB, Bennik J, Heere B, Lesniak D, Davila-Roman VG, Gropler RJ. The effects of plasma insulin and glucose on myocardial blood flow in patients with type 1 diabetes mellitus. *J Am Coll Cardiol* 2005;**46**:42–48.
37. de las Fuentes L, Herrero P, Peterson LR, Kelly DP, Gropler RJ, Davila-Roman VG. Myocardial fatty acid metabolism: Independent predictor of left ventricular mass in hypertensive heart disease. *Hypertension* 2003;**41**:83–87.
38. Vinereanu D, Nicolaides E, Boden L, Payne N, Jones CJ, Fraser AG. Conduit arterial stiffness is associated with impaired left ventricular subendocardial function. *Heart* 2003;**89**:449–450.
39. Von Bibra H, Thrainsdottir IS, Hansen A, Dounis V, Malmberg K, Ryden L. Tissue Doppler imaging for the detection and quantitation of myocardial dysfunction in patients with type 2 diabetes mellitus. *Diab Vasc Dis Res* 2005;**2**:24–30.
40. Diamant M, Lamb HJ, Groeneveld Y, Endert EL, Smit JW, Bax JJ, Romijn JA, de Roos A, Radder JK. Diastolic dysfunction is associated with altered myocardial metabolism in asymptomatic normotensive patients with well-controlled type 2 diabetes mellitus. *J Am Coll Cardiol* 2003;**42**: 328–335.
41. Ceriello A, Taboga C, Tonutti L, Quagliaro L, Piconi L, Bais B, Da Ros R, Motz E. Evidence for an independent and cumulative effect of postprandial hypertriglyceridemia and hyperglycemia on endothelial dysfunction and oxidative stress generation: Effects of short- and long-term simvastatin treatment. *Circulation* 2002;**106**:1211–1218.
42. Dounis V, Siegmund T, Hansen A, Jensen J, Schumm-Draeger PM, von Bibra H. Global myocardial perfusion and diastolic function are impaired to a similar extent in patients with type 2 diabetes mellitus and in patients with coronary artery disease-evaluation by contrast echocardiography and pulsed tissue Doppler. *Diabetologia* 2006;**49**:2729–2740.