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/Ht2.7, in g/m2.7: 34.9 + 6.7, 41.0 + 9.5, 46.3 + 11.0, \( P < 0.001 \)); LV relaxation decreased progressively (Veglobal, 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.

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

Introduction
The metabolic syndrome represents a clustering of cardiovascular risk factors affecting \( \sim 22\% \) 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.3–4 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
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) impaired fasting glucose (≥5.6 mmol/L); (d) decreased HDL-C (<0.45 mmol/L in men or <0.56 mmol/L in women); (e) impaired fasting diastolic dysfunction (L VEF <55%); (f) hypertension (≥140/90 mmHg and/or current antihypertensive therapy).16 Overweight and obesity were defined as a body mass index between 25-30 kg/m² and >30 kg/m², 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 ventricular wall thickness, and L VEF (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: L V end-diastolic diameter / 2 • end-diastolic posterior wall thickness. The LV mass was determined by the M-mode-derived cubed method and indexed to height².⁷ (LVM/Ht²) to correct for body habitus; LVM was defined as LWM/Ht² >51 g/m²² for men and >49.5 g/m²² for women.20 Pulsed-wave Doppler (PWD)-derived transmial 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.22 Tissue Doppler imaging (TDI) was utilized 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.23–25 Measurements included the systolic (Vs) and early diastolic (Ve) myocardial velocities. Values reported include the velocities at the septum (VsSeptal and VeSeptal) and the average of the four annular sites (VsGlobal and VeGlobal). 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 >0.240 ms; (2) TDI criteria: VeGlobal ≤12.9 cm/s if age <40; VeGlobal ≤10.2 cm/s age 40-59; and VeGlobal ≤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 Vsglobal, VeGlobal, and E/A ratio and included: age, LWM/Ht², Vsglobal (except when Vsglobal 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/Ht², 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 Vseptal, but not Vsglobal, (measures of longitudinal systolic myocardial contractility) was significantly lower in the Metabolic Syndrome group compared with the Absent group (P = 0.006). Univariate
analyses showed that systolic and diastolic blood pressure, glucose (only for Vsglobal), triglyceride, age, and LVM/Ht2.7 were significant predictors of Vsseptal and Vsglobal; however, stepwise multiple variable analysis found that only age and LVM/Ht2.7 were independent predictors of Vsseptal (model r² = 0.16), and that age, systolic and diastolic blood pressures were independent predictors of Vsglobal (model r² = 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 Veceptal and Vglobal were significantly lower in both the Metabolic Syndrome and Pre-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 (model r² = 0.16). 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. Vglobal, 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/Ht2.7, and glucose, HDL-C, triglyceride, and metabolic syndrome group assignment (Absent, Pre-Metabolic Syndrome, or Metabolic Syndrome) with covariates including age, LVM/Ht2.7, and triglyceride remained independently associated with Veceptal (r² = 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 ≤ 0.0004).
for all). Stepwise multiple variable regression analyses showed that age, diastolic blood pressure, Vsglobal, 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 Veglobal 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 analyses.

### Table 2  Echocardiographic parameters of LV structure and function

<table>
<thead>
<tr>
<th></th>
<th>Absent ($n = 110$)</th>
<th>Pre-MetS ($n = 311$)</th>
<th>MetS ($n = 186$)</th>
<th>$P$-values</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adjusted Omnibus$^a$</td>
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<tr>
<td><strong>LV structure</strong></td>
<td></td>
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<tr>
<td>LVEDD, mm</td>
<td>48 ± 4</td>
<td>49 ± 5</td>
<td>49 ± 5</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>LVESD, mm</td>
<td>32 ± 4</td>
<td>31 ± 5</td>
<td>32 ± 5</td>
<td></td>
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<tr>
<td>LVEDV, ml</td>
<td>90 ± 23</td>
<td>91 ± 23</td>
<td>92 ± 22</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>LVESV, ml</td>
<td>33 ± 10</td>
<td>32 ± 11</td>
<td>33 ± 11</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>RWT</td>
<td>0.37 ± 0.05</td>
<td>0.40 ± 0.06</td>
<td>0.43 ± 0.08</td>
<td></td>
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<tr>
<td>LVM/HT$^2$, g/m$^2$</td>
<td>34.9 ± 6.7</td>
<td>41.0 ± 9.5</td>
<td>46.3 ± 11.0</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>LA diameter, mm</td>
<td>36 ± 5</td>
<td>38 ± 5</td>
<td>40 ± 6</td>
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<tr>
<td><strong>LV systolic function</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>LVEF, %</td>
<td>64 ± 4</td>
<td>65 ± 6</td>
<td>65 ± 5</td>
<td></td>
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<tr>
<td>Vsglobal, cm/s</td>
<td>8.2 ± 1.1</td>
<td>8.0 ± 1.2</td>
<td>7.7 ± 0.9</td>
<td>0.04</td>
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<tr>
<td><strong>LV diastolic function</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>E-wave, cm/s</td>
<td>72 ± 14</td>
<td>72 ± 16</td>
<td>74 ± 17</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>A-wave, cm/s</td>
<td>48 ± 14</td>
<td>55 ± 15</td>
<td>66 ± 18</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.6 ± 0.5</td>
<td>1.4 ± 0.5</td>
<td>1.2 ± 0.5</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>DT, ms</td>
<td>198 ± 33</td>
<td>202 ± 34</td>
<td>216 ± 40</td>
<td>0.0002</td>
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<tr>
<td>IVRT, ms</td>
<td>88 ± 15</td>
<td>95 ± 19</td>
<td>95 ± 19</td>
<td>0.05</td>
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<tr>
<td>Vseptal, cm/s</td>
<td>11.5 ± 2.4</td>
<td>10.4 ± 2.7</td>
<td>9.0 ± 2.1</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Veglobal, cm/s</td>
<td>13.5 ± 2.8</td>
<td>12.1 ± 3.0</td>
<td>10.5 ± 2.2</td>
<td>$&lt;0.0001$</td>
</tr>
</tbody>
</table>

*aThe omnibus $P$-values are adjusted per Bonferroni.

*bPair-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.
V_{\text{global}} (P < 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 $V_{\text{global}}$ 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: $n = 157$, Pre-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 $V_e$ (data not shown).

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

### 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, $\text{RWT}$ 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. $V_{\text{global}}$) univariate analyses (HDL-C excluded), only diastolic blood pressure, waist circumference, and triglyceride remained independently associated with $V_{\text{global}}$ 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. However, few studies have evaluated the relationship between metabolic syndrome and echocardiographically derived measures of LV structure and function. In the present study, measurements of diastolic ($V_e$) 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, $\text{RWT}$, and deceleration time have been reported in hypertensive subjects with metabolic syndrome compared with a hypertensive cohort without the syndrome. In the Strong Heart Study, those with metabolic syndrome were characterized in Pre-Metabolic Syndrome. The present study, by use of improved measures to detect LV relaxation (i.e. $V_e$), 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 $V_e$ significantly lower in the Pre-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 normal range contribute to diastolic dysfunction.
Progressive abnormalities in LV mass and diastolic dysfunction

Although LV mass exhibited a direct correlation with measures of impaired relaxation (both \( V_e \) and \( E/A \) ratio) in univariate analyses, its predictive value was relatively weak for \( V_e \), selected after age, \( V_e \), 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. 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. 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.
Metabolic syndrome is associated with left ventricular function


