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See Editorial Commentary, pp 762–764

Abstract—Left ventricular (LV) function is generally assessed independent of structural remodeling and vice versa. The purpose of this study was to evaluate a novel LV global function index (LVGFI) that integrates LV structure with global function and to assess its predictive value for cardiovascular (CV) events throughout adult life in a multiethnic population of men and women without history of CV diseases at baseline. A total of 5004 participants in the Multi-Ethnic Study of Atherosclerosis underwent a cardiac magnetic resonance study and were followed up for a median of 7.2 years. The LVGFI by cardiac magnetic resonance was defined by the ratio of stroke volume divided by LV total volume defined as the sum of mean LV cavity and myocardial volumes. Cox proportional hazard models were constructed to predict the end points of heart failure, hard CV events, and a combined end point of all CV events after adjustment for established risk factors, calcium score, and biomarkers. A total of 579 (11.6%) CV events were observed during the follow-up period. In adjusted models, the end points of heart failure, hard CV events, and all events were all significantly associated with LVGFI (heart failure, hazard ratio=0.64, P<0.0001; hard CV events, hazard ratio=0.79, P=0.007; all events, hazard ratio=0.79, P<0.0001). LVGFI had a significant independent predictive value in the multivariable models for all CV event categories. The LVGFI was a powerful predictor of incident HF, hard CV events, and a composite end point, including all events in this multiethnic cohort. (Hypertension. 2013;61:770-778.)

Key Words: ejection fraction ● heart failure ● left ventricle ● LV global function index ● LV mass

Left ventricular (LV) function must be sufficient for adequate oxygen delivery to peripheral organs and tissues. In varying physiological conditions, this is accomplished by modulating heart rate or stroke volume (SV) through several mechanisms. The short-term regulation of SV involves changes in preload, afterload, and contractility, whereas intermediate- and long-term regulation include physiologically and pathologically mediated LV remodeling.1 In pathological situations, this remodeling may affect the LV passive-elastic properties, myocardial mass, and LV chamber size.2 Therefore, the relationship between SV and LV size may carry information about physiological as well as pathological remodeling.

The most frequently used index of LV function in clinical practice,3,4 the LV ejection fraction (LVEF), does not account for the relationship between LV mass and LV dimensions. This might partly explain its limited sensitivity and specificity in various stages of cardiovascular (CV) diseases.5,6 Furthermore, in spite of being an established marker of LV systolic function, LVEF fails to index diastolic dysfunction.7,8 Recently, other LV parameters, such as the LV mass normalized for body size and LV end-diastolic mass/volume ratio (LVMVR), have been shown to be independently associated with CV outcome.9,10 Because stroke volume will vary with heart size in healthy individuals, a relationship between SV and total heart size, including the LV mass and overall LV cavity size (mean of end-diastolic and end-systolic volumes), can be predicted. Patients with congestive heart failure attributable to LV...
systolic dysfunction (LVEF<50%)\textsuperscript{13} frequently have LV dilation with preserved SV, at least initially, before progressive systemic decompensation.\textsuperscript{14} However, congestive heart failure patients with predominant diastolic dysfunction typically have preserved LVEF with smaller LV cavities and thicker walls.\textsuperscript{14,15} Indeed, as previously demonstrated, relationships between SV and LV cavity volume and LV mass differ significantly in patients with predominantly systolic versus diastolic heart failure (HF).\textsuperscript{15} Therefore, an approach integrating LV functional and structural indices is needed for a more

Table 1. Baseline Characteristics of the MESA Study Cohort for Participants With and Without Selected Clinical Events

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Events, n=4425</th>
<th>HF, n=112</th>
<th>Hard CVD, n=216</th>
<th>All Events, n=579</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61±10</td>
<td>68±8</td>
<td>67±9</td>
<td>68±9</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>2015 (46)</td>
<td>75 (67)</td>
<td>133 (62)</td>
<td>367 (64)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1712 (39)</td>
<td>48 (43)</td>
<td>98 (45)</td>
<td>245 (42)</td>
</tr>
<tr>
<td>African American</td>
<td>1111 (25)</td>
<td>35 (31)</td>
<td>53 (25)</td>
<td>174 (30)</td>
</tr>
<tr>
<td>Chinese</td>
<td>604 (14)</td>
<td>5 (4)</td>
<td>14 (6)</td>
<td>49 (9)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>998 (22)</td>
<td>24 (22)</td>
<td>51 (24)</td>
<td>111 (19)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>1748 (40)</td>
<td>82 (73)</td>
<td>143 (66)</td>
<td>372 (64)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>124±21</td>
<td>138±21</td>
<td>138±24</td>
<td>135±23</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>72±10</td>
<td>73±11</td>
<td>75±12</td>
<td>74±11</td>
</tr>
<tr>
<td>Body mass index, kg/m\textsuperscript{2}</td>
<td>28±5</td>
<td>29±5</td>
<td>28±5</td>
<td>28±5</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>478 (11)</td>
<td>34 (30)</td>
<td>50 (23)</td>
<td>116 (20)</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td>2081 (47)</td>
<td>72 (64)</td>
<td>115 (53)</td>
<td>354 (61)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>195±35</td>
<td>190±35</td>
<td>195±35</td>
<td>191±35</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>52±15</td>
<td>49±14</td>
<td>48±14</td>
<td>49±15</td>
</tr>
<tr>
<td>Hypertension medication, n (%)*</td>
<td>1467 (33)</td>
<td>67 (60)</td>
<td>108 (50)</td>
<td>299 (52)</td>
</tr>
<tr>
<td>Lipid-lowering medication, n (%)*</td>
<td>676 (15)</td>
<td>27 (24)</td>
<td>45 (21)</td>
<td>120 (21)</td>
</tr>
<tr>
<td>Left ventricular characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF, %</td>
<td>69±7</td>
<td>64±12</td>
<td>68±8</td>
<td>68±9</td>
</tr>
<tr>
<td>LV mass index, g/m\textsuperscript{2}</td>
<td>77±15</td>
<td>97±27</td>
<td>86±19</td>
<td>85±20</td>
</tr>
<tr>
<td>LV mass/LV volume, g/mL</td>
<td>1.15±0.24</td>
<td>1.30±0.3</td>
<td>1.31±0.27</td>
<td>1.28±0.28</td>
</tr>
<tr>
<td>LVGFI, %</td>
<td>40±7</td>
<td>34±9</td>
<td>36±7</td>
<td>37±7</td>
</tr>
</tbody>
</table>

CVD indicates hard cardiovascular disease events; HDL, high-density lipoprotein; HF, heart failure; LV, left ventricle; LVEF, LV ejection fraction; LVGFI, LV global function index; and LV mass/LV volume, LV mass to end-diastolic volume ratio.

All data are presented as mean±SD, n (%).

*Values are presented for participants taking the medications.
complete and useful phenotypic characterization of cardiac performance throughout the adult lifespan.

In the present study, we propose a global structural and functional index (LVGFI) that combines the LV SV, end-systolic and end-diastolic volumes, as well as LV mass using data from the Multi-Ethnic Study of Atherosclerosis (MESA) obtained during the baseline examination. We evaluate the ability of LVGFI to predict adverse CV events during 7.2±1.5 (mean±SD) years of MESA follow-up and, as secondary end points, we compare the relationship of LVGFI to CV events relative to those of LVMVR, LVEF, and the LV mass index during the follow-up period.

Methods

Study Population

The MESA is a multicenter prospective cohort study of healthy individuals. Details of its methodology have been previously published.16

Cardiac MRI

The complete MRI protocol as well as details on image analysis, data quality control, calculations for LVEF, LV mass and volumes, and reproducibility of these global LV measurements have been published previously.17 LV mass was indexed to body size by dividing the raw LV mass by height raised to the power of 2.7.18

Left Ventricular Global Function Index

The LVGFI was defined for each participant according to the following formula:

\[
LVGFI = \left( \frac{LVSV}{LV \text{ global volume}} \right) \times 100 ,
\]

where LV global volume was defined as the sum of the LV mean cavity volume \( (LVEDV + LVESV)/2 \) and the myocardium volume.

Because LV mass is calculated as the product of LV myocardial volume and myocardial density (1.05 g/mL), myocardial volume was extracted before the calculation of mass. Thus, the corresponding LVGFI value was expressed as a percentage. Interobserver and intraobserver reproducibility levels for LV mass, left ventricular end diastolic volume (LVEDV), left ventricular end systolic volume (LVESV), stroke volume, and LVGFI are reported in the online-only Data Supplement material. The theoretical variation of LVGFI and LVEF in various pathophysiological settings are compared in Figure 1.

A healthy MESA reference population was defined without obesity, hypertension (or hypertension medication use), diabetes mellitus (or diabetes mellitus medication use), smoking habitus, or hypercholesterolemia (high-density lipoprotein cholesterol <40 mg/dL, or lipid-lowering medication use) of study participants (n=857; age 58±10 years; women 60.6%; African American 14.0%, white 40.5%, Chinese 25.0%, Hispanic 20.5%). The distribution of the LVGFI was assessed in the reference group, and the thresholds for quartile distribution in the total MESA population were then set a priori on the values obtained within this reference population.

Cardiovascular Events During the Follow-Up Period

The primary outcome measure for this study was incident symptomatic HF, as defined in previous reports.9 We also assessed 2 secondary outcome measures defined a priori in MESA based on prespecified clinical event definitions: (1) hard CV events, including hard coronary events (myocardial infarction, resuscitated cardiac arrest, and death from coronary disease) plus fatal and nonfatal stroke; (2) combined end point including all previous event categories, in addition to all-cause mortality, angina, and coronary revascularization (percutaneous coronary intervention or coronary artery bypass surgery). In this final category, only the first clinical event was reported for each participant. A precise definition of each individual outcome and adjudication of clinical event for the MESA study are available online (http://www.mesa-nhlbi.org/).

Statistical Analysis

 Detailed description of statistical analyses is reported in the online-only Data Supplement material for this article. All statistical analyses were performed using STATA (version 11.0, College Station, TX), and 2-sided probability values <0.05 was considered to be significant.

Briefly, unadjusted univariable Cox Proportional Hazards Models were used to evaluate the effects of each LV variable on the time-to-event probabilities separately for each of the clinical end points.

Then, in the multivariable survival analysis, the association between LVGFI or all other LV variables and time-to-event was analyzed, adjusting for age, sex, ethnicity, diabetes mellitus, systolic blood pressure, diastolic blood pressure, current smoking, body mass index, antihypertensive or lipid-lowering therapy, high-density lipoprotein-cholesterol, total plasma cholesterol, Agaston coronary calcium score, glomerular filtration rate, C-reactive protein, and N-terminal Pro-B natriuretic peptide.

Results

Clinical Characteristics of the MESA Study Cohort and CV Events

Among the 6814 participants of the MESA cohort, 5000 (73%) underwent a baseline cardiac MRI examination. The baseline characteristics of the study population, according to the presence or absence of CV events, are presented in Table 1. Over a mean follow-up period of 7.2±1.5 years, HF developed in
112 (2.2%) participants, and 216 (4.3%) experienced a hard CV event. Combining all prespecified clinical events together and reporting only the first event for each patient, 579 (11.6%) participants had a CV event in this same time period.

**LVGFI in a Healthy Reference Group Distribution and Relationship to LVEF, LVMVR, and Indexed LV Mass**

First, we assessed the relationship between SV and absolute LV mass and LV mean cavity volume, respectively (Figure 2). The LV SV was closely related to both LV mean cavity size ($R^2=0.65$; $P<0.001$) as well as absolute LV mass ($R^2=0.59$; $P<0.001$). The distribution of LVGFI was left-skewed with a mean of 42±6% and 40±7% for the healthy reference group and the entire study population, respectively. LVEF and LVGFI were significantly correlated in the whole MESA population as shown in Figure 3. The cutoff point for the lower 25th percentile in the healthy reference group was of 37%. The specific characteristics of each LV parameter for participants with and without selected CV events are reported in Table 1.

**Relationship of the LVGFI to Incident HF**

The results of unadjusted and adjusted Cox proportional hazard models are shown in Table 2 for each LV parameter and each clinical end point. Both LVGFI and LVEF were negatively associated with incident HF before and after adjustment for risk factors and biomarkers (after adjustment, LVGFI, hazard ratio [HR]=0.64 per 1 SD increment, $P<0.0001$; LVEF, HR=0.68 per 1 SD increment, $P<0.0001$). LV mass index was positively associated with incident HF (HR=1.29 per 1 SD increment; $P<0.0001$). Importantly, LV mass index was positively associated with incident HF (HR=1.29 per 1 SD increment; $P<0.0001$).

**Table 2. Unadjusted and Adjusted Hazard Ratios of Adverse Clinical Outcome According by the Left Ventricular Global Function Index, Ejection Fraction, Mass to Volume Ratio, and Indexed Left Ventricular Mass**

<table>
<thead>
<tr>
<th>Models</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR, 95% CI</td>
<td>$P$ Value</td>
</tr>
<tr>
<td>Heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVGFI, % (per 1 SD)</td>
<td>0.44 (0.37–0.53)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>LVEF, % (per 1 SD)</td>
<td>0.56 (0.49–0.64)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>LVMVR, g/mL (per 1 SD)</td>
<td>1.51 (1.32–1.72)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>LV mass index (per 1 SD)</td>
<td>1.45 (1.32–1.59)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Hard cardiovascular events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVGFI, % (per 1 SD)</td>
<td>0.60 (0.53–0.68)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>LVEF, % (per 1 SD)</td>
<td>0.88 (0.77–0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>LVMVR, g/mL (per 1 SD)</td>
<td>1.56 (1.42–1.71)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>LV mass index (per 1 SD)</td>
<td>1.45 (1.32–1.59)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>All events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVGFI, % (per 1 SD)</td>
<td>0.60 (0.55–0.65)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>LVEF, % (per 1 SD)</td>
<td>0.81 (0.74–0.88)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>LVMVR, g/mL (per 1 SD)</td>
<td>1.49 (1.40–1.58)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>LV mass index (per 1 SD)</td>
<td>1.76 (1.61–1.91)</td>
<td>$&lt;0.0001$</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HR, hazard ratio; LV, left ventricle; LVEF, LV ejection fraction; LVGFI, LV global functional index; LV mass index, LV mass indexes to height$^{2.7}$; and LVMVR, LV mass to end-diastolic volume ratio.

*All LV parameter values were normalized according to the following formula: (LV parameter–mean value in healthy reference group)/standard deviation in healthy reference group.

Adjusted Model includes age, sex and ethnicity, presence of diabetes mellitus, systolic blood pressure, diastolic blood pressure, current and former smoking, HDL-cholesterol, total cholesterol, logarithm mean Agatston calcium score phantom-adjusted, body mass index (BMI) and current medications (any antihypertensive or lipid-lowering medication), calibrated glomerular filtration rate, logarithm of N-terminal Pro-B natriuretic peptide (NT-proBNP), and logarithm of C-reactive protein (CRP). BMI was not included in the model with indexed LV mass.

**Figure 3. Correlation plots between left ventricular ejection fraction (LVEF) and left ventricular global functional index (LVGFI) in the whole Multi-Ethnic Study of Atherosclerosis (MESA) population. Linear (black line) and nonlinear (dashed line) regression lines are shown. LVEF indicates left ventricular ejection fraction; and LVGFI, left ventricular global functional index.**
LVMVR was not significantly associated with incident HF in the fully adjusted model ($P=0.8$).

When LVGFI was categorized in quartiles, a LVGFI value $<37\%$ was associated with almost a 5-fold increase in the incidence of HF in comparison with the upper 75th percentile ($P<0.0001$) with a significant difference in the cumulative hazard by log-rank test (Figure 4). The other baseline variables with an independent predictive value on the incidence of HF in the multivariate analysis were heart rate (HR=1.04; $P=0.02$), presence of diabetes mellitus (HR=2.58; $P=0.01$), and increased levels of log N-terminal Pro-B natriuretic peptide (HR=2.44; $P<0.0001$).

**Relationship of the LVGFI to Hard CV Events**

LVGFI was also negatively associated with incident hard CV events (nonfatal myocardial infarction, resuscitated cardiac arrest, and death from coronary disease plus fatal and nonfatal stroke before and after adjustment for all other predictors; LVGFI, HR=0.79 per 1 SD increment, $P=0.007$ in the fully adjusted model). When LVGFI was categorized in quartiles, a LVGFI value $<37\%$ was associated with a strong trend of 2-fold increase in the incidence of hard CV disease in comparison with the upper 75th percentile ($P=0.07$), and there was a significant difference in the cumulative hazard by log-rank test (Figure 4). For hard CV events, the adjusted predictive value of LVEF was not significant ($P=0.8$). Both LVMVR (HR=1.27; $P<0.0001$) and the LV mass index (HR=1.20; $P=0.008$) had positive significant predictive values on incident hard CV disease in the fully adjusted model.

**Relationship of the LVGFI to All Events (Composite End Point of Hard CV Events, All-Cause Mortality, Angina, and Coronary Revascularization)**

After adjustment for risk factors and biomarkers, LVGFI was significantly associated with the incident composite end point (LVGFI, HR=0.79 per 1 SD increment, $P<0.0001$), and so was the LVEF (HR=0.89; $P=0.01$). A LVGFI value $<37\%$ was significantly associated with a 60% increase in the composite end point incidence, in comparison with the upper quartile ($P=0.012$) with a significant difference in the cumulative hazard by log-rank test (Figure 4). Moreover, both the LV mass index (HR=1.30; $P=0.001$) and the LVMVR were significantly associated (HR=1.16; $P=0.001$) with the incident composite end point.

**Comparison of Models Performance**

As reported in Figure 5, the area under the curve for the unadjusted predictive value of each LV parameter for each clinical outcome was statistically significant. The area under the curves obtained with LVGFI and LV mass index for HF were significantly greater than those obtained with LVEF and LVMVR ($P<0.0001$). Moreover, for hard CV events and all clinical events combined, the area under the curves obtained with LVGFI, LV mass index, and LVMVR were significantly greater than those obtained with LVEF ($P<0.0001$, respectively). As reported in Figure 6, the area under the curves for the predictive value of each LV parameter as determined in the fully adjusted on each clinical outcome was not significantly
different, when the LV parameter remained independently significant in the model. For incident HF, LVMVR was not significantly associated and for incident hard CV events, LVEF was not significantly associated. This indicates that only LVGFI and indexed LV mass remained independent significant predictors for all clinical outcomes.

Results from the ranking of each model and its corresponding LV parameter with the Akaike Information Criterion are presented in Table 3. For incident HF, the best model was obtained with LVEF; for incident hard CV events, the best model fit was obtained with LVMVR, and for the composite clinical end point, the best model was obtained with LVGFI (Table 3). This suggests that, as LVGFI integrates LV remodeling as well as LV systolic performance information, it is a more comprehensive and reliable predictor of combined CV events.

Discussion

The current study demonstrates that in a large multiethnic cohort without symptoms of CV disease at enrollment, the LVGFI that integrates structure and function is independently associated with the subsequent development of HF, hard CV events, and a combined end point of all adverse events. Furthermore, a LVGFI <37% confers between 1.5- and 2-fold of risk for incident HF, total mortality, and combined adverse atherosclerotic events over a mean follow-up of 7.2 years. Although LVEF, LVMVR, and LV mass index provided risk stratification for different types of incident adverse clinical end points similar to the LVGFI; when a fully adjusted multivariate model was used, LVGFI remained the most robust predictor in all 3 categories. This suggests that LVGFI is a more reliable LV functional index because it reflects cardiac performance for different degrees of structural LV remodeling.

Our results show that defining a new functional index combining LV global systolic performance information with anatomic LV parameters affected by remodeling is efficient. Although the LVGFI is strongly related to LVEF, it carries additional information that makes it more robust than LVEF, LVMVR, and LV mass for predicting different categories of CV events. With the development of new and more reliable imaging techniques, cardiac remodeling classified as isolated cardiac hypertrophy or as hypertrophy in combination with LV dilation, has received recent attention in the quest for defining better prognostic and therapeutic targets, particularly in the setting of preclinical CV diseases.1,2 Our results support the hypothesis that LV remodeling and performance is best described by a combination of structural and functional parameters. Another important finding of this study resides in the intrinsic value of each LV parameter to predict different categories of CV events. As shown in Figure 5, the integration of SV, LV volumes, and LV mass in a single multidimensional parameter, improves the stability of the predictive index over different categories of CV events.

The limits of LVEF, the most used LV functional index in clinical routine, are clearly shown here, with its lower intrinsic value across all event categories except HF. LVEF is a basic global functional marker of systolic function that has become a cornerstone for routine risk stratification and therapeutic strategy decision in patients with CV disease.10,20 However, this
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A parameter has been criticized recently on its lack of sensitivity and specificity to predict subsequent adverse CV events.5 This is particularly true at the subclinical stages of CV disease and was clearly shown in the CHARMES study in diastolic HF patients, where LVEF was not a significant predictor of death and HF hospitalization.8 One reason might be that significant LVEF changes appear later in the pathological process and are preceded by significant compensatory modifications in LV mass and volumes to preserve systolic function. This is true in untreated hypertensive patients where LVEF remains unchanged across a broad range of increasing hypertension categories, despite significant increase in LV wall stress and LV wall thickness.21 LVEF does not account for important predictors of remodeling, such as LV mass, and this might be one reason why the novel global function index remains significant in all conditions, whereas LVEF is not.

The limitations of LVMVR for the prediction of incident HF events, however, are also demonstrated. In diastolic HF, LVMVR values are significantly increased, whereas they remain in the normal range for systolic HF.14 On the contrary, indexed LV mass had the highest intrinsic predictive value for HF events, and this can be explained by the significance of LV hypertrophy as an important compensatory mechanism in both systolic (eccentric remodeling) and diastolic (concentric remodeling) HF.1

Several studies have demonstrated associations between LV remodeling, including indexed LV mass and end-diastolic volumes to CV events.9–12,22 In a recent report from the MESA study, Bluemke et al9 showed that LV mass and LV mass-to-volume ratio adjusted to body size with a complex allometric approach were both independently predictive of HF events and stroke. Our HRs and significance level results in the same population confirm the powerful independent predictive value of LV mass with the limited predictive value of LVMVR on HF events. Conversely, LVMVR remained a significant independent predictor of hard CV events (mainly atherosclerotic in nature) possibly by better reflecting the overall CV fibrosis process, but possibly also by lowering the threshold for symptoms in the setting of myocardial ischemia, cerebrovascular occlusion, and nonfatal myocardial infarction.

This study also supports the concept that normalized LV mass measured by MRI is a very strong predictor of adverse CV

<table>
<thead>
<tr>
<th>LV Functional Parameter</th>
<th>CHF</th>
<th>Hard Cardiovascular Events</th>
<th>All Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVGFI, %</td>
<td>1332</td>
<td>2709</td>
<td>7062</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>1328</td>
<td>...</td>
<td>7076</td>
</tr>
<tr>
<td>LVMVR ratio, g/mL</td>
<td>...</td>
<td>2705</td>
<td>7069</td>
</tr>
<tr>
<td>LV mass index</td>
<td>1336</td>
<td>2710</td>
<td>7072</td>
</tr>
</tbody>
</table>

CHF indicates congestive heart failure; LVEF, LV ejection fraction; LVGFI, left ventricular global functional index; LV mass index, LV mass was indexed to height raised to the power of 2.7; and MV ratio, mass to end-diastolic-volume ratio.

Akaike Information Criterion (lower is better) for each LV parameter was obtained with Model 2 (full model).

Figure 6. Receiver operating characteristic (ROC) curves of the predictive power of left ventricular global functional index (LVGFI), left ventricular ejection fraction (LVEF), LV end-diastolic mass/volume ratio (LVMVR), and left ventricular (LV) mass index determined with a multivariate Cox-regression model on the presence/absence of the different clinical outcome categories (Heart Failure Events, A; Hard CV Events, B; All CV Events, C). There were no significant differences between the different areas under the curve (AUC) obtained with each LV parameter (P=NS). The ROC curves were not computed if the predictive value of the LV parameter did not reach significance level <0.05 in the full multivariable regression model. LVEF indicates left ventricular ejection fraction; LVGFI, left ventricular global functional index; LVMVR, left ventricular mass to end-diastolic volume ratio; and normalized LV mass, LV mass normalized by body surface area.
and despite being a weaker predictor of events than the LVGFI for total combined events, it was the only index that remained significant in the presence of LVGFI throughout all end point categories in the full multivariate model. The power of LV mass normalized by body size is, in large part, secondary to its place in the causation pathway of multiple CV disease processes, including hypertension, diabetes mellitus, ischemia, obesity, and inflammation. This was also shown with LVGFI for total combined events, it was the only index that included information of physiological adaptation as well as pathological remodeling by measures of both cavity size and myocardial mass. Average cavity volume was chosen as a marker of cavity size that reflects the LV operating volume, and not one of the extra-ventricular-like LVEDV or LVESV, and thus should serve as an improved measure of overall cavity size.

Limitations

The general applicability of our results may be limited by selection and survivor biases. Because MESA participants had no known CV disease at baseline, the older individuals undergoing MRI in this cohort represents a healthier sample than the general population at large. Finally, the mechanisms by which CV events are associated with changes in LV structure and function are not entirely elucidated by these observational data. These markers may, however, provide important clues to the pathophysiology of untoward CV outcomes.

Perspectives

In an ethnically diverse population free of symptomatic CV disease at baseline, the LV global function index is strongly associated with adverse CV events during follow-up, whereas LVEF is not associated with hard CV events beyond HF. These results suggest that a functional parameter (LVGFI) that integrates structural as well as mechanical behavior may have utility both in the prediction of subsequent CV events, and also in providing insight into the pathophysiology of different CV outcomes.

Acknowledgments

We thank Elzbieta Chamera, Drs Masamichi Imai and Sanaz Samiei for their invaluable contribution in the preprocessing of MRI images, Karen Hansen for her valuable contribution in this manuscript’s administrative processing, and the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

Sources of Funding

The National Heart, Lung, and Blood Institute supported this project (contracts N01-HC-95159 through N01-HC-95169). The French Federation of Cardiology supported Dr Nathan Meleton with a Post-Doctoral Research Grant at the Johns Hopkins Hospital. The Raagholt Research Foundation supported Dr Anders Opdahl with a Post-Doctoral Research Grant at the Johns Hopkins Hospital. The Norwegian Cardiovascular Society supported Dr Anders Opdahl with a Post-Doctoral Research Grant at the Johns Hopkins Hospital. The Musaeus Aarsvold Foundation supported Dr Anders Opdahl with a Post-Doctoral Research Grant at the Johns Hopkins Hospital. The US–Norway Fulbright Foundation supported Dr Anders Opdahl with a Post-Doctoral Research Grant at the Johns Hopkins Hospital. The Sorensen Research Foundation, Oslo, Norway, supported Dr Anders Opdahl with a Post-Doctoral Research Grant at the Johns Hopkins Hospital.

Disclosures

None.

References

Hypertension impacts LV structure before it alters LV function.

Novelty and Significance

**What Is New?**

- The combination of left ventricular (LV) mass, volumes, and stroke volume in a single left ventricular global functional index (LVGFI) integrating all the dimensions of the LV functional anatomy is new.
- The LVGFI was strongly and consistently associated with adverse cardiovascular (CV) events during follow-up across various categories of CV events.
- If the LVGFI predictive power was comparable with indexed LV mass alone, it was more powerful and consistent than LV mass-to-volume ratio and LV ejection fraction (LVEF).

**What Is Relevant?**

- Hypertension impacts LV structure before it alters LV function.

**Summary**

In an ethnically diverse population free of symptomatic CV disease at baseline, the LVGFI is strongly associated with adverse CV events during follow-up, whereas LVEF is not associated with hard CV events beyond heart failure.

**What Is Relevant?**

- It is essential to have a reliable and reproducible assessment of LV structure and function for the therapeutic management of hypertensive patients.
- The LVGFI or indexed LV mass should be integrated on a routine basis in the CV risk, as well as therapeutic management of hypertensive patients.

Nathan Mewton, Anders Opdahl, Eui-Young Choi, Andre L.C. Almeida, Nadine Kawel, Colin O. Wu, Gregory L. Burke, Songtao Liu, Kiang Liu, David A. Bluemke and Joao A.C. Lima

Hypertension. 2013;61:770-778; originally published online February 19, 2013;
doi: 10.1161/HYPERTENSIONAHA.111.198028

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/61/4/770

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Left Ventricular Global Function Index By Magnetic Resonance Imaging- A Novel Marker for Assessment of Cardiac Performance for the Prediction Of Cardiovascular Events: The Multi-Ethnic Study of Atherosclerosis

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Methods

Study population.

The MESA (Multi-Ethnic Study of Atherosclerosis) study is a multicenter prospective cohort study of healthy individuals of different ethnicity and older than 45 years old from 6 U.S. communities in Maryland, Illinois, North Carolina, California, New York, and Minnesota between July 2000 and August 2002. The study was designed to examine the prevalence, associated factors and progression of subclinical cardiovascular disease. All participants had no known clinical cardiovascular disease at enrollment. Details of its rationale and methodology have been previously published. Informed consent was obtained from each participant.

Cardiac MRI

Consenting eligible participants underwent cardiac magnetic resonance imaging at enrollment. The complete MRI protocol has been detailed previously.

The LV mass, LV end-diastolic volume (EDV), end-systolic volume (ESV) and stroke volume (SV) were determined for each participant using dedicated, commercially available software (MASS, version 4.2, Medis, Leiden, The Netherlands) as described previously.

The LV mass to end-diastolic volume ratio (LVMVR) was determined by unadjusted LV mass/EDV-ratio as previously described. Details on image analysis, data quality control, calculations for LVEF, LV mass and volumes and reproducibility of these global LV measurements have been published previously.

Cardiovascular Events during the Follow-up Period

A telephone interviewer contacted each participant (or representative) every 6 to 9 months to inquire about all interim hospital admissions, cardiovascular outpatient diagnoses, and deaths. In addition, all participants underwent 3 follow-up MESA examinations. Medical records and information were successfully obtained on an estimated 98% of hospitalized cardiovascular events and 95% of outpatient cardiovascular diagnostic encounters. Two physicians from the MESA morbidity and mortality committee blinded to cardiac MRI findings reviewed all records for independent end point classification and assignment of event dates.

The primary outcome measure for this study was incident symptomatic heart failure (HF) as defined in prior reports. We also assessed two secondary outcome measures defined a priori in MESA based on pre-specified clinical event definitions: 1) hard cardiovascular events including hard coronary events (myocardial infarction, resuscitated cardiac arrest and death from coronary disease) plus fatal and nonfatal stroke; 2) combined endpoint including all previous event categories in addition to all cause mortality, angina and coronary revascularization (percutaneous coronary intervention or coronary artery bypass surgery). Only the first clinical event was reported for each participant. A precise
definition of each individual outcome and adjudication of clinical event for the MESA study are available online (http://www.mesa-nhlbi.org/).

**Statistical Analysis**

Continuous variables with approximately normal distributions are presented as mean ± SD, and variables which are skewed or clearly non-normally distributed are reported as median (interquartile range). The linear relationship between SV and LV mass or LV mean cavity volume was assessed by univariable linear regression. The linear relationship between LVGFI and LVEF was assessed by the Pearson’s correlation coefficient.

In order to compare the statistical results for the four different LV variables under a unified scale, we used normalized LV variables; for a variable X, the normalized value is \((X-\mu)/\sigma\), where \(\mu\) and \(\sigma\) are the mean and standard deviation of X, respectively, for the healthy reference group. Unadjusted univariable Cox Proportional Hazards Models were used to evaluate the effects of each LV variable on the time-to-event probabilities separately for each of the clinical endpoints.

Then, in the multivariable survival analysis, the association between LVGFI or all other LV variables and time-to-event was analyzed adjusting for age, gender, ethnicity, diabetes, systolic blood pressure, diastolic blood pressure, current smoking, body mass index, antihypertensive or lipid lowering therapy, HDL-cholesterol, total plasma cholesterol, Agaston coronary calcium score, Glomerular Filtration Rate, CRP, and NT-proBNP. Variables with skewed distribution (Agatston calcium score, CRP and NT-proBNP) were log-transformed by taking natural logarithm before inclusion in the multivariate analysis. For the Agatston score, we used the value \((CAC\text{score}+1)\) before log-transformation.

Categorical variables were generated by dividing LVGFI in quartiles, using the thresholds obtained in the group of healthy participants without any cardiovascular risk factors. The highest LVGFI quartile was set as reference for all the other quartile groups. Cumulative hazards of each clinical time-to-event endpoint for the different LVGFI quartiles were illustrated in Nelson-Aalen plots and were compared using the log-rank test.

We tested and compared the discrimination ability of LVGFI, LV mass indexed to height\(^2\), LVEF and LVMVR for major cardiac events in the univariate and multivariate analyses beyond, through differences in area under the curve (AUC) derived from ROC analysis. AUCs were computed based on the predicted risk from Cox hazards modeling and compares using a parametric method. The best fit for each LV indicator in the full model adjusted model and for each outcome was also assessed by the Akaike information criterion (AIC).\(^5\) All statistical analyses were performed using STATA (version 11.0, College Station, TX, USA) and two sided p-values <0.05 was considered to be significant.
Results Supplements

LVGFI inter- and intra-observer reproducibility

Technologist interobserver variability was measured in 50 MR readings selected at random (2% of the entire cohort) by comparing the original MR volumes and mass readings with results from a second review performed between 3 months later. Intraobserver variability was assessed in 50 MR readings performed in the same manner. Reviewers were blinded to the results of the initial reading at the time of the second readings.

Left Ventricular Global Function Index in a healthy reference group- distribution and relationship to LVEF, LVMVR and indexed LV mass.

The LVGFI distribution was left-skewed with a mean of 42±6% and 40±7% for the healthy reference group and the entire study population, respectively. The cutoff point for the lower 25th percentile in the healthy reference group was of 37%. In this same healthy control population, mean LVEF was of 70±6% and the cutoff point for the 5th percentile was of 59%; the mean LV mass-to-volume ratio was of 1.06 ± 0.19 g/mL, and the 95th percentile cutoff point was of 1.39 g/mL. The mean normalized LV mass was of 66 ± 10 g/m² in female participants and 82 ± 13 g/m² in male participants. In those cases, the 95th percentile cutoffs were 85 g/m² and 105 g/m² for females and males respectively.
Supplemental References


Supplemental Tables

Table S1: Inter-observer Variability for Left Ventricular (LV) mass, volumes and LVGFI measurements.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number of readings</th>
<th>Mean (Mean)</th>
<th>Difference (Mean)</th>
<th>Difference (Standard Deviation)</th>
<th>95% Limits of Agreement</th>
<th>Intra class Correlation</th>
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</thead>
<tbody>
<tr>
<td>LVEDV (ml)</td>
<td>50</td>
<td>122.9</td>
<td>-1.9</td>
<td>5.0</td>
<td>-11.6; 7.8</td>
<td>0.98</td>
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<tr>
<td>LVESV (ml)</td>
<td>50</td>
<td>41.3</td>
<td>-1.5</td>
<td>10.4</td>
<td>-21.9; 18.9</td>
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<td>LV Mass (g)</td>
<td>50</td>
<td>129.3</td>
<td>1.5</td>
<td>4.1</td>
<td>-6.6; 9.6</td>
<td>0.99</td>
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<tr>
<td>LV Stroke Volume (ml)</td>
<td>50</td>
<td>81.6</td>
<td>-1.2</td>
<td>6.5</td>
<td>-13.9; 11.5</td>
<td>0.92</td>
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<td>LVGFI (%)</td>
<td>50</td>
<td>40.4</td>
<td>-1.0</td>
<td>2.2</td>
<td>-5.4; 3.3</td>
<td>0.90</td>
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</tbody>
</table>

Note—LV = left ventricle; EDV = end-diastolic volume; ESV = end-systolic volume; LVGFI = left ventricular global function index.
Table S 2: Intra-observer Variability for Left Ventricular (LV) mass, volumes and LVGFI measurements

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number of readings</th>
<th>Mean Difference (Mean)</th>
<th>Difference (Standard Deviation)</th>
<th>95% Limits of Agreement</th>
<th>Intra class Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDV (ml)</td>
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<td>120.6</td>
<td>-1.1</td>
<td>5.3</td>
<td>-11.6; 9.4</td>
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<td>LVESV (ml)</td>
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<td>3.2</td>
<td>-6.9; 5.7</td>
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<td>LV Mass (g)</td>
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<td>0.6</td>
<td>5.6</td>
<td>-10.4; 11.6</td>
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<tr>
<td>LV Stroke Volume</td>
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<td>76.4</td>
<td>-0.5</td>
<td>3.8</td>
<td>-8.0; 7.0</td>
</tr>
<tr>
<td>LVGFI (%)</td>
<td>50</td>
<td>39.9</td>
<td>-0.2</td>
<td>1.7</td>
<td>-3.6 ; 3.2</td>
</tr>
</tbody>
</table>

Note—LV= left ventricle; EDV = end-diastolic volume; ESV = end-systolic volume; LVGFI = left ventricular global function index.
Supplemental Figures

Fig S1: Bland Altman Plot Analysis For the Independent Inter-Reader Reproducibility of LVGFI. LVGFI: left ventricular global function index. Obs1: reader 1. Obs2: reader 2.
Fig S 2: Bland Altman Plot Analysis For the Intra-Reader Reproducibility of LVGFI. LVGFI: left ventricular global function index. Obs1: reader 1.