Does Information on Systolic and Diastolic Function Improve Prediction of a Cardiovascular Event by Left Ventricular Hypertrophy in Arterial Hypertension?

Giovanni de Simone, Raffaele Izzo, Marcello Chinali, Marina De Marco, Giuseppina Casalnuovo, Francesco Rozza, Daniela Girfoglio, Gianni Luigi Iovino, Bruno Trimarco, Nicola De Luca

Abstract—Left ventricular (LV) mass (LVM) is the most important information requested in hypertensive patients referred for echocardiography. However, LV function also predicts cardiovascular (CV) risk independent of LVM. There is no evidence that addition of LV function significantly improves model prediction of CV risk compared with LVM alone. Thus, composite fatal and nonfatal CV or cerebrovascular events were evaluated in 5380 hypertensive outpatients (2336 women, 298 diabetics, and 1315 obese subjects) without prevalent CV disease (follow-up: 3.5±2.8 years). We compared 5 risk models using Cox regression and adjusting for age and sex: (1) LV mass normalized for height in meters².7 (LVMi); (2) LVMi, concentric LV geometry, by relative wall thickness (>0.43), ejection fraction, and transmitral diastolic pattern (by thirtiles of mitral deceleration index); (3) LVMi, LV geometry, midwall shortening, and mitral deceleration index thirtiles; (4) as No. 2 with the addition of left atrial dilatation (>23 mm); and (5) as No. 3 with the addition of left atrial dilatation. Individual hazard functions were compared using receiving operating characteristic curves and z statistics. Areas under the curves increased from 0.60 in the model with the sole LVMi to 0.62 in the others (all P values for differences were not significant). The additional information on systolic and diastolic function decreased the contribution (Wald statistics) of LVMi in the Cox model without improving the model ability to predict CV risk. We conclude that risk models with inclusion of information on LV geometry and systolic and diastolic function, in addition to LVMi, do not improve the prediction of CV events but rather redistribute the impact of individual predictors within the risk variance. (Hypertension. 2010;56:99-104.)

Key Words: cardiac mass ■ heart atria ■ cardiovascular risk ■ arterial hypertension ■ prognosis ■ outcome ■ hazard models

Despite the most common recommendation to perform echocardiographic examinations in hypertensive patients based on indications that might yield modifications of the management strategy1,2 and the most recent guidelines that do not list echocardiography in the primary workup for arterial hypertension, arterial hypertension remains one of the most frequent indications for echocardiography, especially in countries where the direct cost is not perceived as a direct charge for patients.

The substantial reason for echocardiography in arterial hypertension is assessment of left ventricular (LV) mass, based on the broad evidence that LV hypertrophy (LVH) is one of the most important prognostic markers in hypertension, as well as in general populations.3,4 However, following the reports on LVH, a large number of studies have indicated other echocardiographic markers of cardiovascular risk to be independent of LVH, including LV geometry5,6 and systolic and diastolic function.7–10 The demonstration of independence from LVH is usually obtained using multivariate Cox proportional hazard analysis, which highlights all of the independent predictors in a given model. However, the analysis of Cox regression model does not respond to the question of whether the addition of parameters of LV geometry and function in a model improves the overall model prediction compared with LVH alone or, rather, redistributes the risk prediction on more predictors, leaving unchanged the overall ability of the model to predict cardiovascular risk. Accordingly, we compared the overall accuracy of Cox models to predict composite cardiovascular and cerebrovascular events in a large population sample of hypertensive outpatients, prospectively studied, including or excluding parameters of cardiac geometry and function with LV mass.

Methods

Population Study

The cohort of outpatients of the Campania Salute Network was analyzed. Details on this cohort have been reported previously.11,12 Briefly, the Campania Salute Network is an open registry collecting...
information from a network of general practitioners and community hospitals connected with the center and providing patients with a smart card including demographics and clinical information.

In the subcohort of 10,254 patients with arterial hypertension, individuals in sinus rhythm with a follow-up of ≥6 months and free of prevalent cardiovascular or cerebrovascular disease were selected (n = 5,380). Prevalent cardiovascular disease was defined at the first examination in the outpatient clinic and included previous myocardial infarction, angina, procedures of coronary revascularization, stroke, transient ischemic attack, or congestive heart failure.

Incident composite fatal and nonfatal cardiovascular or cerebrovascular events were used as end points of the present analysis, including fatal or nonfatal acute coronary syndrome requiring hospitalization, fatal or nonfatal stroke, and transient ischemic attack. Prevalent and incident cardiovascular and cerebrovascular diseases were adjudicated by the Committee for Event Adjudication in the Hypertension Center and were based on patient history, contact with the reference general practitioner, and clinical records documenting the occurrence of disease.11,12

The database generation of the Campania Salute Network was approved by the Federico II University Hospital Ethic Committee. Signed informed consent for the possibility of using data for scientific purposes was obtained.

**Procedures**

Diabetes mellitus and obesity were identified according to current guidelines13 recommendations. All of the hypertensive patients of the network undergo the baseline echocardiogram at the time of the first examination. All of the echocardiograms were performed using commercially available phased-array machines between 1990 and 2008 and were processed and read offline by one expert reader in the Hypertension Center under the supervision of a senior faculty member. Primary measures were entered into the database and derived parameters calculated thereafter.

LV mass was measured according to standard Devereux-modified American Society of Echocardiography formula14 and normalized by height in meters raised to the allometric power of 2.7.15 LV hypertrophy was defined as LV mass index >46.7 g/m2.7 in women or 49.2 g/m2.7 in men. Relative wall thickness was generated as 2-times posterior wall thickness divided by LV diastolic dimension and used to identify concentric LV geometry (for values >0.43).16 LV systolic function was assessed as both ejection fraction, computed using the z-derived method of computation of LV volumes,17 and midwall shortening, as reported previously in detail.18 Measurement of diastolic function was performed by pulsed-Doppler interrogation of transmural blood flow, which has been prognostically validated in previous studies,19,20 although its independence of other prognostic markers remains uncertain. Peak mitral early (E) and late (A) velocities were measured at the tips of mitral leaflets and used to calculate the E/A ratio. The ratio of deceleration time of E velocity to peak E velocity (defined as mitral deceleration index [MDI]) has been used as another marker of diastolic dysfunction, which has been shown to predict CV outcome even better than the E/A ratio.19,20 Both measures of diastolic function were categorized in tertiles. Left atrial (LA) linear antero-posterior dimension recorded in parasternal long-axis view and normalized for height (LA dimension index) was also used as a raw index of chronic diastolic dysfunction.21 To identify LA dilatation, we used the partition value of 23 mm, as suggested.22

**Statistical Analysis**

Descriptive statistics are presented as mean±1 SD or as median and interquartile range, when assumption of normal distribution was not met, or as χ2 distribution. Five models of proportional hazard regression (Cox) are presented, adjusted for age and sex and including the following: (1) LV mass normalized for height in meters2.7 (LVMi); (2) LVMi, categories of relative wall thickness defining normal or concentric LV geometry, ejection fraction, and diastolic function based on tertiles of MDI (using simple contrast and the middle tertile as the reference category); (3) as above but with midwall shortening instead of ejection fraction; (4) as No. 2 with the addition of LA dimension categories (ie, normal or dilated); and (5) as No. 3 with the addition of LA dimension categories (ie, normal or dilated). Alternative models were run using categories of E/A ratio instead of MDI. Wald statistics were used to evaluate the relative weight of LV mass index inside each Cox model. For each Cox regression, individual hazard functions were generated and compared using receiving operating characteristic curves, and the areas under the curves (AUCs) were calculated and compared using z statistics,23 without correction for multiple comparisons, to minimize the probability of a type 1 error. Detection of a significant difference between 2 AUCs indicates significant difference in the overall ability of the prediction, with the largest area indicating the best predictive model. Failure to detect significant differences among the AUCs denotes similar predictive ability of the models with a redistribution of the pattern of the risk within the predictive model when additional variables enter the regression.

**Results**

Table 1 displays the general characteristics of this population and gives information on the distribution of obesity, diabetes mellitus, and LV hypertrophy. The analyzed hypertensive population presented a broad range of age, a relatively low prevalence of obesity, and a low prevalence of diabetes mellitus but a relatively high prevalence of LV hypertrophy. A total of 170 patients experienced incident events (corresponding with an incident rate of 0.84 events per 100 person-years), 114 cardiovascular events (22 were fatal, with an incident rate of 0.56 events per 100 person-years), and 56 cerebrovascular events (3 were fatal, with an incident rate of 0.28 events per 100 person-years). Procedures of elective revascularization not related to acute coronary syndrome and, therefore, classified as primary end points, were censored in 38 patients (22%).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Range</th>
<th>Mean±1 SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up, y</td>
<td>0.50 to 10.99</td>
<td>3.46±2.83</td>
</tr>
<tr>
<td>Age, y</td>
<td>17.06 to 89.03</td>
<td>52.84±11.47</td>
</tr>
<tr>
<td>Sex, men/women</td>
<td>3014/2336</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>15.43 to 67.19</td>
<td>27.69±4.21</td>
</tr>
<tr>
<td>Obesity, n (%)</td>
<td>1315 (25)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>298 (6)</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>100.0 to 210.0</td>
<td>140.98±19.68</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>45.0 to 133.0</td>
<td>78.99±11.25</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>37.5 to 125.0</td>
<td>71.82±11.88</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>88.53 to 586.09</td>
<td>189.22±41.07</td>
</tr>
<tr>
<td>LV mass index, g/m²×7</td>
<td>23.04 to 116.35</td>
<td>47.37±9.59</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.25 to 0.85</td>
<td>0.41±0.04</td>
</tr>
<tr>
<td>LWH, n (%)</td>
<td>1759 (31)</td>
<td></td>
</tr>
<tr>
<td>LA dimension, mm</td>
<td>22.00 to 61.00</td>
<td>37.46±3.71</td>
</tr>
<tr>
<td>LA dimension index, mm/m</td>
<td>12.64 to 38.13</td>
<td>22.46±2.27</td>
</tr>
<tr>
<td>LA dilatation, n (%)</td>
<td>1056 (20)</td>
<td></td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>34.18 to 83.95</td>
<td>65.64±3.97</td>
</tr>
<tr>
<td>Midwall shortening, %</td>
<td>6.95 to 26.88</td>
<td>16.52±1.75</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.31 to 11.00</td>
<td>0.99±0.32</td>
</tr>
<tr>
<td>Mitral deceleration index</td>
<td>0.43 to 7.76</td>
<td>2.56±0.85</td>
</tr>
</tbody>
</table>
The unadjusted risk of incident cardiovascular events was 2-fold greater in patients with than in those without LV hypertrophy (hazard ratio [HR]: 2.03 [95% CI: 1.51 to 2.75]; P<0.0001; Figure 1, left). Adjustment for age and sex maintained a 1.54-fold greater risk of CV events in patients with LVH (P<0.005). Similarly, LA dilatation was associated with 1.84 greater risk (95% CI: 1.35 to 2.50; P<0.0001; Figure 1, right), and adjustment for age and sex attenuated but did not eliminate the risk pattern (P<0.03). In contrast, in this population of treated and unselected hypertensive patients, concentric LV geometry was not significantly associated with greater risk (HR: 1.33 [95% CI: 0.89 to 1.97]).

The highest thirtile of the E/A ratio (ie, ≥1.06) was associated with >40% reduction of CV risk (HR: 0.57 [95% CI: 0.34 to 0.95]) compared with the middle thirtile (ie, 0.83 to 1.05; P<0.04), whereas the lowest thirtile (ie, <0.83) was associated with a 2-fold greater risk (HR: 1.99 [95% CI: 1.36 to 2.92]; P<0.0001; Figure 2, left). Similarly, the highest thirtile of MDI (ie, ≥2.62) was associated with 2-fold greater risk (HR: 2.07 [95% CI: 1.38 to 3.07]) than the reference middle thirtile (ie, 2.00 to 2.61; P<0.0001), whereas no difference was found between the lowest (ie, <2.00) and the middle thirtiles (Figure 2, right).

Table 2 displays the Wald statistics of LV mass index after adjusting for age and sex compared with the additional Cox models also including categories of LV geometry, ejection fraction, or midwall shortening and the pattern of LV filling, estimated by thirtiles of MDI and LA dimension index. The addition of other echocardiographic variables into the predictive model based on LV mass index caused a progressive reduction of the Wald statistics of LV mass index and a redistribution of the pattern of the risk.

The hazard functions of the 5 regression equations were, therefore, compared using receiving operating characteristic curves, and the AUCs were compared. Figure 3 shows that the 5 curves were similar and that the CIs of the receiving operating characteristic curves were nearly identical. Thus, no statistically significant differences could be demonstrated among the curves, even without adjustment for multiple comparisons.

The analysis has been repeated also using thirtiles of the transmitral peak E/A ratio instead of MDI, but the results did not change (data not shown). Also, excluding the 38 elective revascularization procedures from the composite end point did not change the results (data not shown).

**Discussion**

There is large evidence that, even in the absence of prevalent CV disease, many parameters obtainable by standard trans-thoracic echocardiograms influence prognosis, often independent of LV hypertrophy.5–10 LV concentric geometry and LV dysfunction (both systolic and diastolic) are among the most studied. These parameters, however, have obvious biological (and mathematical, as well) collinearity with LV mass, and
their apparent independent prognostic effect might be simply part of the explained effect of LV mass. There is no information in the literature about whether consideration of parameters of LV geometry and function in the Cox models, in addition to identifying other independent prognostic predictors, also increases the ability to predict cardiovascular risk. Often the result of these multiple regressions exhibiting additional independent effect of parameters different from LV mass is considered as substantial to improve our ability to predict CV risk. However, this inference does not consider the possibility that the entry of other echocardiographic variables in the predictive regression does not alter the final accuracy of the predictive model but simply redistributes the individual predictive weight among the independent variables inside the model, leaving the overall accuracy unchanged compared with the model including the sole LV mass.

Diastolic dysfunction is evaluated using thirtiles of the ratio of deceleration of E velocity to peak E velocity (MDI), with the middle value as the reference value.

FS indicates fractional shortening.

### Table 2. Wald Statistics of Age- and Sex-Adjusted Cox Models Including Different Echocardiographic Predictors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model With Only LVMi</th>
<th>Model With Ejection Fraction and Diastolic Pattern</th>
<th>Model With Midwall FS and Diastolic Pattern</th>
<th>Model With Ejection Fraction, Diastolic Pattern, and LA Dimension</th>
<th>Model With Midwall FS, Diastolic Pattern, and LA Dimension</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV mass index, g/m²⁻⁷</td>
<td>14.90</td>
<td>11.83</td>
<td>11.19</td>
<td>8.21</td>
<td>7.58</td>
</tr>
<tr>
<td>LV concentric geometry</td>
<td></td>
<td>1.20</td>
<td>2.80</td>
<td>1.07</td>
<td>2.65</td>
</tr>
<tr>
<td>LV systolic function, %</td>
<td></td>
<td>4.06</td>
<td>3.33</td>
<td>4.17</td>
<td>3.54</td>
</tr>
<tr>
<td>Low MDI, &lt;2</td>
<td></td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>High MDI, &gt;2.62</td>
<td></td>
<td>2.74</td>
<td>2.64</td>
<td>2.91</td>
<td>2.80</td>
</tr>
<tr>
<td>LA dilatation, &gt;23 mm</td>
<td></td>
<td>1.01</td>
<td>0.316</td>
<td>1.10</td>
<td>0.294</td>
</tr>
</tbody>
</table>

LV mass index is considered as substantial to improve our ability to predict CV risk. However, this inference does not consider the possibility that the entry of other echocardiographic variables in the predictive regression does not alter the final accuracy of the predictive model but simply redistributes the individual predictive weight among the independent variables inside the model, leaving the overall accuracy unchanged compared with the model including the sole LV mass.

Diastolic dysfunction is evaluated using thirtiles of the ratio of deceleration of E velocity to peak E velocity (MDI), with the middle value as the reference value.

FS indicates fractional shortening.

### Hazard Functions

Figure 3. Receiving operating characteristic curves and areas under the curves for cumulative hazard functions of LV mass index, as well as the addition of indicators of LV geometry, diastolic and systolic function, and LA dilatation. eFS indicates endocardial fractional shortening; mFS, midwall fractional shortening.
In the present study, in addition to LV mass index, LA dilatation and diastolic dysfunction are also significantly associated with increased CV risk, consistent with a number of previous observations, whereas we did not find effect of LV concentric remodeling, in contrast with previous findings in high-risk hypertensive geometry. However, this study demonstrates that the addition of parameters of LV geometry and function, as well as consideration of LA dilatation, reduces the specific weight of LV mass in the model but does not alter the final overall accuracy of prediction. Not surprisingly, in this population sample selected on the basis of absence of clinically overt cardiovascular disease, LV systolic function but not diastolic function was confirmed to be a predictor of CV disease also in multivariate analysis, independent of LV mass index, but its effect was included in the information obtained by considering only LV mass. Additional considerations emerge from our results.

First of all, despite the biological plausibility of the finding, indicating that information on LV mass includes prognostically relevant information on LV geometry and function, the parameters of LV diastolic function that we used in this analysis are only raw estimates of LV filling pattern. More advanced ultrasound techniques (early transmural flow propagation, pulmonary vein flow velocities, tissue-Doppler imaging, 2D-strain imaging, etc.) could give different results. Unfortunately, at this time, there is no wide availability of longitudinal cohort studies including this information. However, in our analysis, LA dilatation was also considered as a marker of chronic diastolic dysfunction, which was associated with CV outcome as strongly as was LV mass index (see Figure 1). However, when considered together with LV mass, the effect of LA dimension appeared to be incorporated into the information gained from LV mass, similar to all of the other parameters. Assessment of LA volume could possibly give more information, but in epidemiological studies the simple assessment of LA dimension is also informative. In the Cardiovascular Health Study, LA dilatation (by volume) was always associated with the increase in antero-posterior dimension, and the ratio between antero-posterior and the supero-inferior dimension was only marginally altered in hypertensive subjects compared with healthy controls.

Secondly, there is an important implication from our findings concerning the potential of extending the echocardiographic examination to all hypertensive patients, a wish common to many hypertension specialists. The time required to compute LV mass (also including relative wall thickness) is limited. In our laboratory, the average time needed to receive the patient (2 operators), accommodate her/him on the bed, obtain an ECG trace, perform a long-axis view with the primary linear measurements to derive measures of LV geometry and function from 3 cardiac cycles, and measure blood pressure thereafter is 10 to 15 minutes. Thus, if targeted on assessment of LV geometry, a limited echocardiogram might be extended to many hypertensive subjects, and identification of clear-cut LV hypertrophy may also suggest associated early abnormalities in LV function in addition to being a strong marker of CV outcome.

Perspectives

Thus, LV mass is confirmed as the most potent bioassay of CV abnormality in arterial hypertension, incorporating the harmful effect of systolic and diastolic dysfunction. The present analysis does not contradict the pathophysiological value of many studies on systolic and diastolic dysfunction, addressed to clarify mechanisms of impairment of LV performance, but rather indicates that, at the time of the initial evaluation of hypertensive patients, the simplest measure of LV mass is sufficient to model effective risk prediction, which might be helpful in clinical practice. Whether more recent ultrasound techniques and/or computation of LA volume might add to the prediction of CV risk obtained by assessment of LV mass should be tested in large population with available tissue-Doppler interrogation and LA volumes measurements. The effect of antihypertensive therapy over time and the ability to change the model of prediction should also be evaluated in future studies.

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Disclosures

None.

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