Epidemiology—Left Ventricular Mass and Cognition

Left Ventricular Mass, Blood Pressure, and Lowered Cognitive Performance in the Framingham Offspring

Merrill F. Elias, Lisa M. Sullivan, Penelope K. Elias, Ralph B. D’Agostino, Sr, Philip A. Wolf, Sudha Seshadri, Rhoda Au, Emelia J. Benjamin, Ramachandran S. Vasan

Abstract—The purpose of this study was to determine whether echocardiographic left ventricular mass is related to cognitive performance beyond casual blood pressure adjusting for the influence of other vascular risk factors. We used multivariable regression analyses to relate left ventricular mass assessed at a routine examination (1995–1998) to measures of cognitive ability obtained routinely (1998–2001) in 1673 Framingham Offspring Study participants (56% women; mean age: 57 years) free from stroke, transient ischemic attack, and dementia. We adjusted for the following covariates hierarchically: (1) age, education, sex, body weight, height, interval between left ventricular mass measurement and neuropsychological testing (basic model); (2) basic model + blood pressure + treatment for hypertension; and (3) basic model + blood pressure + treatment for hypertension + vascular risk factors and prevalent cardiovascular disease. For the basic model, left ventricular mass was inversely associated with abstract reasoning (similarities), visual-spatial memory and organization, and verbal memory. For the basic model + blood pressure + treatment for hypertension, left ventricular mass was inversely associated with similarities and visual-spatial memory and organization. For the basic + blood pressure + treatment for hypertension + risk factors + cardiovascular disease model, no significant associations were observed. Echocardiographic left ventricular mass is associated with cognitive performance beyond casual and time-averaged systolic blood pressure, but this association is attenuated and rendered nonsignificant with additional adjustment for cardiovascular risk factors and cardiovascular disease, thus suggesting that these variables play an important role in mediating the association between left ventricular mass and cognition. (Hypertension. 2007;49:439-445.)

Key Words: left ventricular mass ▶ blood pressure ▶ cognitive performance ▶ cardiovascular risk factors ▶ cardiovascular disease

Although there is an extensive literature on the association of blood pressure and cognitive performance, little information is available regarding the relationship of left ventricular mass (LVM) to cognition. With regard to blood pressure (BP), many studies have shown that, over a wide range of BP values and with adjustment for hypertension-related complications, both systolic and diastolic BP are inversely related to the level of cognitive performance and longitudinal decline in performance.1–9 The most widely accepted mechanism by which high BP reduces cognitive ability is via its effect on brain structure and function.10–16 Hypertension is associated with acceleration of atherosclerosis in the large arteries and is associated with medial thickening of the intracerebral vessels leading to cerebral white matter hypoperfusion and ischemic rarefaction.16 A causal association between higher BP and lower cognition has been suggested because of the observation of a “dose–response” effect in studies relating BP and cognition.1–3,7–9

Both the duration and the magnitude of BP elevation have been related inversely to cognitive performance.9 However, the use of the duration of hypertension as a marker of the chronic hemodynamic burden posed by high BP is challenged by the lack of precision in identifying the exact date of hypertension onset in epidemiological studies. LVM is strongly associated with long-term BP cross-sectionally10 and is a predictor of future risk of hypertension in nonhypertensive individuals11. In addition, LVM is a surrogate marker of cardiovascular target organ damage and is associated with incidence of cardiovascular disease prospectively.12–16 These findings suggest that LVM, as determined by echocardiography, should relate to levels of cognitive performance in a manner similar to, but not necessarily identical with, BP.

Because LVM is a time-integrated correlate of exposure to BP and to other cardiovascular risk factors, it may serve as a marker of the chronicity and the degree of BP elevation and an indicator of long-term burden of vascular risk factors.
Moreover, the strong association of LVM with vascular disease\textsuperscript{12–16} leads to the hypothesis that LVM is inversely related to cognitive functioning. The finding of an association between higher LVM and lower cognitive performance may strengthen the hypothesis that long-term exposure to high BP results in subclinical brain injury, which, in turn, results in lower levels of cognitive performance.

Surprisingly, few studies have related LVM or left ventricular hypertrophy to objective measures of cognitive performance. In the Helsinki Aging Study, LVM was associated with a 5-year decline in Mini-Mental State Examination scores for 160 elderly participants.\textsuperscript{17} For younger individuals, one would expect a similar relation between LVM and cognition if chronic BP burden affects brain function and, hence, cognition. Given previous findings of a continuous association between LVM and cardiovascular morbidity and mortality in complicated and uncomplicated hypertension,\textsuperscript{12,18,19} our investigation focused on a range of LVM values in relation to cognitive functioning.

In this study we related LVM to cognitive performance in the large community-based Framingham Offspring Study sample (mean age: 57 years; SD = 9). Our hypotheses were as follows: (1) LVM is inversely related to cognitive performance; (2) the significant association between LVM and cognitive performance is partially but not completely explained by time-averaged BP; (3) adjustment of relations between LVM and cognitive performance for time-averaged BP, cardiovascular risk factors, and cardiovascular disease (CVD) will further attenuate relations between LVM and cognitive performance. If hypothesis 3 is confirmed, it would suggest that cardiovascular risk factors and CVD play an important role in the relation between LVM and cognition.

**Methods**

**Study Sample**

The design and sampling procedures for the Framingham Offspring Study have been described previously.\textsuperscript{20} Using a standardized medical interview and physical examination, participants are examined for CVD risk factors and CVD every 4 years. Participants who attended examination 6 (referred to as the index examination), attended examination 7 (and who wished to use a clinically relevant index of depressed mood).\textsuperscript{27,28} Studies Depression Scale distribution was highly skewed, and we wished to use a clinically relevant index of depressed mood.\textsuperscript{27,28} Prevalent CVD included the presence of $\geq 1$ of the following: coronary heart disease (myocardial infarction, angina pectoris, and coronary insufficiency), intermittent claudication, and heart failure. Prevalence or history of CVD was established by a panel of 3 physicians using the relevant clinical data.\textsuperscript{29} Because there was variation among individuals in the time between measurements of LVM and neuropsychological testing, an LVM–neuropsychological testing interval (LVM-NT) variable was constructed by calculating for each participant the years (and fractions of a year) between measurement of LVM and neuropsychological testing.

In the primary analysis, the CVD risk factors and CVD were determined at examination cycle 6. In a set of secondary analyses, these were determined at the time of neuropsychological testing (examination cycle 7).

**Neuropsychological Test Performance**

The neuropsychological test battery has been described in detail previously\textsuperscript{30} and is briefly described in Table 1. The battery has been practiced for future stroke in a previous investigation in the Framingham offspring cohort.\textsuperscript{31} A detailed description of each test may be found in Lezak et al.\textsuperscript{32} For each test score, the distribution of original (raw) test scores was standardized to $z$ scores by subtracting the mean of the distribution of raw scores from each individual raw score and dividing by the sample SD. This linear transformation does not change the distribution of scores but allows all of the scores to be expressed in SD units.

After confirmatory factor analyses, we used composite scores derived previously from the application of principal components analysis and orthogonal (Varimax) rotation to the multiple individual
TABLE 1. Description of the Cognitive Tests Administered to the Participants of the Framingham Offspring Study (1971–2005)

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>From the Wechsler Adult Intelligence Scale</td>
<td>Abstract reasoning</td>
</tr>
<tr>
<td>From the Wechsler Memory Scale</td>
<td>New verbal learning and memory</td>
</tr>
<tr>
<td>Paired associates learning</td>
<td>Immediate recall of verbal passages</td>
</tr>
<tr>
<td>Logical memory–immediate recall</td>
<td>Immediate recall of verbal passages</td>
</tr>
<tr>
<td>Logical memory–delayed recall</td>
<td>Delayed recall of verbal passages</td>
</tr>
<tr>
<td>Logical memory–delayed recognition</td>
<td>Delayed recognition of verbal passages</td>
</tr>
<tr>
<td>Visual reproductions–immediate recall</td>
<td>Immediate recall of visual/spatial stimuli</td>
</tr>
<tr>
<td>Visual reproductions–delayed recall</td>
<td>Delayed recall of visual/spatial stimuli</td>
</tr>
<tr>
<td>Visual reproductions–delayed recognition</td>
<td>Delayed recognition of visual/spatial stimuli</td>
</tr>
<tr>
<td>From the Hooper Visual Organization Test</td>
<td>Visual organization with some demands on executive function</td>
</tr>
<tr>
<td>From the Haltstead–Reitan Battery</td>
<td>Visual organization with some demands on executive function</td>
</tr>
<tr>
<td>Trail-making A</td>
<td>Attention, concentration, visual scanning, and speed of tracking</td>
</tr>
<tr>
<td>Trail-making B</td>
<td>Attention, concentration, visual scanning, and speed of tracking; demands on executive function</td>
</tr>
</tbody>
</table>

Statistical Analyses Plan

Descriptive statistics were generated for each LVM measure for demographic characteristics and covariates (including means and SDs for continuous variables and percentages for categorical variables). Multivariable regression models with linear and categorical variables were used to examine the associations between the LVM measures (independent variable) and cognitive performance (dependent variable).

The multivariable regression coefficients relating LVM and LVM-z (standardized LVM) to cognition were adjusted for 3 sets of covariates: (1) basic: age, height, weight, education, sex, and interval between the measurement of LVM and neuropsychological testing (LVM-NT interval); (2) basic + BP + treatment for hypertension; and (3) basic + BP + treatment for hypertension + risk factors (diabetes mellitus, total cholesterol/high-density lipoprotein cholesterol, alcohol consumed per week, cigarettes smoked per day, plasma homocysteine concentration, and depressed mood) + prevalent CVD. A separate regression analysis was performed for each measure of BP, systolic BP at examination cycle 6, mean systolic BP, diastolic BP at examination cycle 6, and mean diastolic BP.

In a secondary set of analyses, described later, risk factor, CVD, and BP variables were based on data gathered at the time of neuropsychological testing (examination 7). A 2-sided P value (P<0.05) was considered statistically significant.

Results

The primary LVM measures included LVM in grams (LVM-g) and LVM-z. LVM-z was computed by subtracting the mean LVM-g score from each LVM-g score and dividing by the SD of LVM-g. These standardized scores (z-scores) were calculated separately for men and women by subtracting the respective sex-specific means and dividing by the respective sex-specific SD. This linear transformation is useful for model interpretation, because regression coefficients reflect that change in cognitive performance relative to a similar increment (1 SD change) in LVM for both men and women.

Descriptive Data

Table 2 contains descriptive statistics for the covariates used in the present study. The mean and SD values for LVM-g were 164.3 and 45.3 for the sex-pooled sample, respectively. Mean values for LVM-g were significantly lower for the women (140.8; SD = 30.7) than for the men (194.6; SD = 43.1; P<0.0001). The sex-specific LVM-z transformation resulted in a mean of z = 0 and SD of z = 1 for men, women, and the sex-pooled samples.

Relations Between LVM and Cognition

We examined the distributional properties of the echocardiographic and the cognitive performance measures. LVM-g was...
TABLE 3. Regression Coefficients (β) and SEs Expressing Associations Between 1 SD Increments in LVM (LVM-z) and Cognitive Performance in Units of SD (z Scores)

<table>
<thead>
<tr>
<th>Cognitive Test Scores</th>
<th>Regression Coefficient or SE</th>
<th>Model Covariates</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Basic* With Exam 6 SBP</td>
<td>With Mean SBP</td>
<td>Basic + BP + Treatment for Hypertension</td>
<td>With Exam 6 SBP</td>
</tr>
<tr>
<td>Similarities</td>
<td>β -0.062†</td>
<td>-0.058†</td>
<td>-0.055†</td>
<td>-0.033</td>
<td>-0.031</td>
</tr>
<tr>
<td></td>
<td>SE 0.026</td>
<td>0.026</td>
<td>0.026</td>
<td>0.028</td>
<td>0.028</td>
</tr>
<tr>
<td>Visual–spatial memory and organization</td>
<td>β -0.071‡</td>
<td>-0.063§</td>
<td>-0.061§</td>
<td>-0.033</td>
<td>-0.032</td>
</tr>
<tr>
<td></td>
<td>SE 0.020</td>
<td>0.021</td>
<td>0.021</td>
<td>0.022</td>
<td>0.022</td>
</tr>
<tr>
<td>Verbal memory</td>
<td>β -0.047†</td>
<td>-0.045</td>
<td>-0.042</td>
<td>-0.034</td>
<td>-0.033</td>
</tr>
<tr>
<td></td>
<td>SE 0.023</td>
<td>0.024</td>
<td>0.024</td>
<td>0.025</td>
<td>0.025</td>
</tr>
<tr>
<td>Scanning and tracking</td>
<td>β -0.041</td>
<td>-0.034</td>
<td>-0.029</td>
<td>-0.027</td>
<td>-0.022</td>
</tr>
<tr>
<td></td>
<td>SE 0.022</td>
<td>0.023</td>
<td>0.023</td>
<td>0.023</td>
<td>0.023</td>
</tr>
<tr>
<td>Paired associates</td>
<td>β -0.003</td>
<td>-0.004</td>
<td>-0.004</td>
<td>-0.006</td>
<td>-0.006</td>
</tr>
<tr>
<td></td>
<td>SE 0.026</td>
<td>0.026</td>
<td>0.026</td>
<td>0.028</td>
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</tbody>
</table>

*Basic covariate set is age, education, sex, height, weight, and LVM-NP interval.
†P<0.05; †P<0.001; §P<0.01.

When relations between LVM-z and cognitive performance were adjusted for the basic+BP+treatment for hypertension+risk factor+CVD covariate set, regression coefficients relating LVM-z to cognition were further attenuated, and no significant relations between LVM-z and cognitive performance were observed. The pattern of significant associations between LVM-z and cognitive performance was similar when mean diastolic BP was substituted for mean systolic BP in the regression models. A table describing results with mean diastolic BP in the regression models may be seen in the supplemental data (available online at http://hyper.ahajournals.org). Findings were the same when BP, treatment for hypertension, CVD risk factors, and CVD were based on data obtained at the time of neuropsychological testing.

Inspection of the regression coefficients (Table 3) expressing the relation between LVM-z and cognitive performance scores provides information with regard to the magnitude of associations. For example, with adjustment for mean systolic BP, each 1 SD increment in LVM (30.7 g in women and 43.1 g in men) was associated with a 0.06-SD decrement in performance level for the similarities score (β = -0.055) and a 0.06-SD decrement for the visual–spatial memory and organization composite score (β = -0.061). In Figures 1 and 2, we illustrate the inverse linear relation between LVM-z and similarities and for visual–spatial memory and organization adjusted for the variables in the basic+mean systolic BP+treatment for hypertension covariate set. The regression lines represent a plot of the predicted values for cognitive performance for SD increments in LVM.

Additional Analyses

Please see the online data supplement for tables summarizing each of the following additional analyses. When treatment for hypertension was deleted from the 2 models that included
either systolic or diastolic BP, the same significant relations between LVM-z and similarities and LVM-z and visual–spatial memory and organization were observed with slightly larger regression coefficients. To determine whether our findings were unique to our method of adjusting for height and weight, we constructed a second measure of LVM, that is, LVM/height, and repeated the analyses above (with height removed from each of the regression models). The pattern of relations between LVM/height and cognitive performance was the same.

Although LVM is the central feature of the present study, it is important to determine whether BP, a crucial covariate in the analyses, was, in fact, related to the cognitive measures for all of the models that include LVM and treatment for hypertension. Mean systolic BP (examination cycles 1 to 6) was related to the following measures of cognitive performance with adjustment for the basic covariate set: visual–spatial memory and organization ($\beta = -0.042; P < 0.05$), verbal memory ($\beta = -0.046; P < 0.05$), and scanning and tracking ($\beta = -0.042; P < 0.05$). It was related to the following measures of cognitive performance with adjustment for the basic+LVM+treatment for hypertension+risk factors+CVD covariate set: verbal memory ($\beta = -0.047; P < 0.05$) and scanning and tracking ($\beta = -0.040; P < 0.05$). The same result was obtained when mean systolic BP was calculated on the basis of BP values from examinations 1 to 7.

**Discussion**

Consistent with our first hypothesis, we observed an inverse association between measures of LVM and cognitive performance in our middle-aged-to-elderly community-based sample. With adjustment for the basic covariate set (age, education, sex, weight, height, and the LVM-NP interval), LVM-z was related to similarities, visual–spatial memory and orga-
nization, and verbal memory. The alternative LVM/height measure was also related to these measures and additionally to the scanning and tracking composite. Generally, our observations are consistent with the finding that LVM, adjusted for age and sex, was associated with a 5-year decline in Mini-Mental State Examination scores for a sample of persons ≥75 years of age in the Helsinki study.17

We now focus on findings with respect to the adjustment of LVM-z for systolic BP. When either examination 6 systolic BP or time-averaged systolic BP was added to the basic covariate set, including treatment for hypertension, relations between LVM-z and cognitive performance were attenuated, but LVM-z continued to be related significantly to similarities (an index of abstract reasoning ability) and visual–spatial memory and organization. The relation between LVM-z and verbal memory was rendered nonsignificant by adjustment for mean systolic BP and treatment for hypertension, but attenuation of the regression coefficient was minor. These observations are consistent with our second hypothesis that relations between LVM and cognition are not completely explained by time-averaged systolic BP. One possible reason why there is a residual association of LVM and cognitive performance, regardless of adjustment for time-averaged or examination-specific systolic BP, is that LVM also serves as a sensitive indicator of lifelong exposure to BP-related risk factors and CVD.12,16,18,19

Indeed, consistent with our third hypothesis, with adjustment for the basic+BP+treatment for hypertension+risk factors+CVD covariate set, all of the relations between LVM-z and cognition were attenuated and rendered nonsignificant. When LVM/height was substituted for LVM-z, the same results were obtained. This finding suggests that the risk factors and CVD events used in our analyses play an important role in the relation between LVM and cognition.

It seems reasonable to hypothesize that similar, although not identical, pathophysiological mechanisms may mediate the associations of lowered cognitive performance with both LVM and BP. For example, both BP and LVM may be surrogate markers of subclinical atherosclerosis in the cerebrovascular territory.13 Yet the observation that, unlike LVM-z, mean systolic BP was related to the verbal memory and scanning and tracking composites for the LVM+BP+treatment for hypertension+RF+CVD model suggests a dissimilarity with respect to ≥1 mechanism mediating relations among LVM, systolic BP, and cognition. This is speculative and, thus, is a hypothesis for further studies involving neuroimaging methods and other cognitive domains as outcome variables.

The relations among LVM and cognition were modest and, thus, may not reflect clinically significant deficits at an individual level. For example, for the basic model, a person 2 SD above the mean of LVM-g would show a 0.24-SD decrement in performance on the visual–spatial memory and organization composite score relative to a person 2 SD below the mean of LVM-g. Nevertheless, as emphasized in the BP1,4,5,9 and dementia23 literature, even small decrements in cognitive ability of individuals are significant from an epidemiological and public health perspective, that is, these modest decrements may progress to more serious forms of deficit.23

Limitations
Several limitations of our study merit comment. Framingham Offspring Study participants are relatively well educated.30 It is well known that education is protective with respect to cognitive performance decrement.34 It is also possible that persons with more extreme LVM values did not participate in our study because of several factors, including early mortality, exclusion of participants with stroke, and the requirement to attend an ancillary study for neuropsychological testing. However, higher levels of education and survivorship very likely contribute to an underestimation of the association of LVM with cognition. The Framingham offspring sample consists of mostly white individuals, thereby limiting the generalizability of our findings to other ethnic/racial groups.

Finally, LVM was assessed on average 3.5 years before neuropsychological performance. Hence, we cannot exclude the possibility that the LVM may have changed in the interim. Nevertheless, as has been true for previous studies of BP,8,9 LVM exhibited a prospective association with lowered cognitive performance.

Perspectives
In stroke- and dementia-free individuals, echocardiographic LVM is associated inversely with cognitive performance, but these associations are attenuated with adjustment for mean systolic BP. They are further attenuated and rendered statistically nonsignificant with adjustment for mean systolic BP, cardiovascular risk factors, and cardiovascular events. Additional studies are warranted to confirm our findings, particularly in cohorts with longitudinal BP data collection and multiethnic samples with a wider education range. Studies identifying mediators of the relations between LVM and cognition (eg, as identified by brain imaging) are particularly important. Overall, the association of LVM with cognition suggests that lifelong exposure to vascular risk factors may adversely influence cognitive performance in later years, because LVM is regarded as an indicator of time-integrated exposure to vascular risk factors (including BP) and subclinical target organ damage as a consequence of such exposure. Although our data are observational, they are consistent with the concept that LVM is a risk marker for lower cognitive performance and that prevention and treatment of vascular risk factors throughout the life course may be associated with better cognitive performance in older age.

Acknowledgments
We express our appreciation to Greg Dore for his assistance in technical aspects of article preparation and copy editing and to Amanda Goodell and Anna Sweeney (all from the University of Maine) for their diligent assistance in copy editing.

Sources of Funding
Support was provided from the Framingham Heart Study of the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH; contract N01-HC25195) and research grants to the Boston University School of Medicine, NIH/National Institute on Aging grant 5RO1-AG08122, NIH/National Institute on Aging grant 5RO1-AG16495, NIH/National Institute of Neurological Disorders and Stroke grant 5RO1-NS17950, NIH/NHLBI grants NO1-HC-25195, NIH/NHLBI grant 1RO1-HL081290, NIH/NHLBI grant 1RO1-HL67358, the Boston University Alzheimer’s Disease...
Center (grant P30 AG13846), RO1 HL 080124, and an NIH mid-career investigator award (2K24HL004334) to R.S.V.

Disclosures

None.

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Hypertension. 2007;49:439-445; originally published online January 15, 2007;
doi: 10.1161/01.HYP.0000256361.68158.24

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

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