Left ventricular mass increase is associated with cognitive decline and dementia in the elderly independently of blood pressure

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Received 18 December 2008; revised 5 March 2009; accepted 12 March 2009; online publish-ahead-of-print 30 April 2009

Aims

Left ventricular (LV) mass increase is considered part of composite target organ damage in hypertension and an independent risk factor for cardiovascular (CV) events. This study was designed to explore whether left ventricular mass index (LVMI) is associated with cognitive decline and dementia in elderly subjects, independently of blood pressure (BP) levels.

Methods and results

Four hundred subjects (mean age 79 ± 6 years) were studied. Left ventricular mass was measured echocardiographically in accordance with American Society of Echocardiography and normalized for body height to the 2.7 (LVMI). Global cognitive function was evaluated with the mini-mental state examination (MMSE) (maximum score 30). Dementia was defined as an MMSE score < 21. Arterial stiffness was evaluated as carotid–femoral pulse wave velocity by Complior®. Prevalence of hypertension was 70% and diabetes mellitus was diagnosed in 25%. No significant differences in traditional CV risk factors were observed across LVMI quartiles. Mini-mental state examination showed an inverse trend across LVMI quartiles (the higher the LVMI, the lower the MMSE, P for trend < 0.05); systolic and diastolic BP levels were not different across LVMI quartiles. In multivariable logistic regression models, including age, sex, BP levels, and use of antihypertensive drugs as covariates, the highest LVMI was found to be independently associated with a two-fold higher likelihood of having dementia. The association persisted significant even after adjustment for arterial stiffness.

Conclusion

In elderly subjects, LVMI is associated with a progressive cognitive decline. This association is independent of BP levels and/or large artery stiffness.

Keywords

Left ventricular mass ● Blood pressure ● Dementia ● Cognition ● Arterial stiffness ● Pulse wave velocity ● Elderly

Introduction

Older subjects are characterized by an increased prevalence and a poorer control of hypertension.1,2 Elevated blood pressure (BP) is recognized to increase left ventricular (LV) mass and occurrence of LV hypertrophy.3,4 This target organ damage is associated with increased risk of cardiovascular (CV) events.5,6

Advancing age is also characterized by progressive cognitive decline and increased risk for dementia, which significantly impacts on loss of personal independence.7 The prevalence of dementia increases with advancing age, affecting ~7% of subjects > 65 years and 30% of those > 80 years.8,9

Age-associated cognitive decline has traditionally been attributed to a neurodegenerative aetiology. This paradigm has been challenged by recognition of the increasing prevalence of microvascular subcortical disease10–12 and by observations that hypertension represents a potent risk factor for Alzheimer dementia.13,14

Increased LV mass (LVM) represents a manner of target organ damage in older subjects, particularly in those affected by hypertension.15 Another clinically relevant marker of target organ...
damage is large artery stiffness, as measured by carotid–femoral pulse wave velocity (PWV). Additionally, increased arterial stiffness has been associated with a higher LVM and risk of LV hypertrophy. Of note, increased PWV has been found both cross-sectionally and longitudinally to be an independent significant determinant of cognitive performance in older subjects.

Therefore, the aims of the present study were to evaluate: (i) whether increased LVM was accompanied by poorer cognitive performance in older subjects, (ii) whether such an association was independent of BP levels, and (iii) whether such an association is not affected by large artery stiffness.

**Methods**

**Study population**

Four hundred patients (mean age 79±6 years) were enrolled in this study. They were consecutive patients who visited the Unit of Geriatrics, IRCCS/INRCA in Rome for evaluation of CV system and/or cognitive functions. After informed consent was signed, all patients underwent a medical history, a clinic visit, urinalysis, blood studies, electrocardiography, and echocardiography. In this group of patients, we also evaluated risk factors such as age, sex, presence of diabetes, plasma lipids, smoking habits, and heart rate. To exclude cognitive decline secondary to nutritional or endocrine alteration, thyroid hormones, vitamin B12, and folate levels were measured in the blood by standard laboratory methods.

Office BP was measured by a physician using a mercury sphygmomanometer after the subjects had rested for 10 min, according to standard procedures. Mean BP was defined as diastolic BP + 1/3(systolic – diastolic BP). Patients were classified as hypertensive if they were routinely taking antihypertensive medications or if the average of three measurements was >140 mmHg for systolic and/or >90 mmHg for diastolic BP. Patients with secondary hypertension, documented permanent or paroxysmal atrial fibrillation, other major illness or those for whom a good-quality echocardiographic recording could not be obtained were excluded from the study.

**Echocardiographic measurements**

All echocardiographic studies were performed with an Agilent Sonos 5500 ultrasound machine. Echocardiograms (parasternal and apical views) were obtained at rest with the patients supine in the left lateral position. The overall one-dimensional LV measurements and the two-dimensional views were obtained according to the recommendations of the American Society of Echocardiography.

Left ventricular mass was estimated by the formula of Devereux et al.: 

\[
\text{LVM (g)} = 0.832 \times [(\text{LVID} + \text{IVS} + \text{PWT})^3 - (\text{LVID}d)^3] + 0.6
\]

where LVM is the left ventricular mass, LVIDd the left ventricular internal dimension at end-diastole, IVS the ventricular septal thickness at end-diastole, and PWT the left ventricular posterior wall thickness at end-diastole. Left ventricular mass was normalized for body height to the 2.7 (LVMI). The presence of LV hypertrophy was defined as an LVMI >50 g/m².7 in either sex.

**Assessment of pulse wave velocity and carotid plaque**

Arterial stiffness was assessed non-invasively by the carotid–femoral PWV. Pulse wave velocity was measured by an automatic device (Complior®, Artech-Medical, France), whose validation and reproducibility have been published previously. Pulse transit time was determined as the average of 10 consecutive beats. The distance travelled by the pulse wave was measured over the body surface as the distance between the two recording sites (carotid and femoral pulse). Pulse wave velocity was calculated as the ratio of distance to transit time. The reproducibility of PWV in our laboratory was evaluated by performing repeated measurements in 20 subjects (6 men and 14 women) with an average age of 67±13 years (range 40–88). The correlation between repeated measurements was 0.92. The mean difference between the two measurements was 0.08 m/s (P=0.73).

High-resolution B-mode carotid ultrasonography was performed by using a linear-array 5–7.5 MHz transducer. The subject lay in the supine position in a dark, quiet room. The stabilized BP after 15 min from the onset of testing was used for subsequent analyses. The right and left common and internal carotid arteries were examined with the head tilted slightly upward in the mid-line position. Carotid plaque was defined as focal encroachment of the arterial wall in any of the explored arterial segments. For the purpose of the present study, plaque was scored as: 0, no plaque; 1, plaque without calcification; 2, plaque with calcification; and 3, stenosis >50% of any explored arterial segment. Carotid plaque measurements were available for 323 subjects only.

**Assessment of global cognitive function**

Global cognitive function was assessed by mean of the mini-mental state examination (MMSE) test. Mini-mental state examination score ranges from 0 to 30, the lower the score the greater the cognitive impairment. Conventionally, a score <24 indicates compromised cognitive function. To increase the accuracy of our analysis, we used an MMSE score <21 to categorize subjects with dementia.

**Statistical analysis**

All analyses were performed via SPSS 8.0 for Windows. Data are presented as means ± SD, unless otherwise specified. χ² analysis was used for categorical variables and Student’s t-test was used for continuous variables. ANOVA was adopted to compare variables across LVMI quartiles. ANCOVA was adopted to compare groups after adjustment for age, sex, traditional CV risk factors, and antihypertensive drugs considered as covariates. Logistic regression models were constructed to identify determinants of dementia (defined as an MMSE score <21). A P-value of <0.05 was considered statistically significant.

**Results**

The study population consisted of 400 subjects (70% women) with an age ranging from 62 to 95 years (mean age 79 years). Hypertension was observed in 70% and diabetes mellitus in 24.5% of the study population; the prevalence of echocardiographically assessed LV hypertrophy was 73.7%.

To analyse the possible role of LVMI as a determinant of cognitive performance in older subjects, subjects were grouped according to LVMI quartiles. As summarized in Table 1, no significant differences in hypertension or diabetes prevalence were observed across LVMI quartiles, nor in traditional CV risk factors levels. With regard to antihypertensive and cardioactive drugs, there was a progressively higher use of calcium channel blockers across LVMI quartiles together with different antiplatelet drugs consumption. Mini-mental state examination showed an inverse trend across LVMI quartiles (the higher the LVMI, the lower the MMSE, P for trend <0.01) (Figure 1, left panel), although systolic and diastolic BP levels were comparable across LVMI quartiles (Figure 1, right panel).
This trend remained significant after adjustment for age, sex, traditional CV risk factors levels, and prevalent cardio- and cerebrovascular disease.

We further analysed whether LVMI increase was an independent determinant of dementia in our study population. Higher occurrence of dementia was observed with increasing LVMI quartiles ($\chi^2 8.9, P < 0.01$). When multivariable logistic regression models were constructed including age, sex, mean BP levels, and use of antihypertensive drugs as covariates, the highest LVMI was found to be independently associated with a 2.7-fold higher likelihood of having dementia when compared with the lowest LVMI quartile (Table 2). The trend remained virtually unchanged.

### Table 1: Demographic and cardiovascular risk profile according to LVMI quartiles

<table>
<thead>
<tr>
<th></th>
<th>1st quartile</th>
<th>2nd quartile</th>
<th>3rd quartile</th>
<th>4th quartile</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>77.4 ± 6.6</td>
<td>78.4 ± 5.2</td>
<td>78.9 ± 5.8</td>
<td>79.9 ± 5.9</td>
<td>0.06</td>
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<tr>
<td>Female sex (%)</td>
<td>60.3</td>
<td>78.2</td>
<td>75.6</td>
<td>78.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Previous MI (%)</td>
<td>6.4</td>
<td>9.2</td>
<td>10.4</td>
<td>15.3</td>
<td>0.32</td>
</tr>
<tr>
<td>Previous stroke (%)</td>
<td>1.3</td>
<td>1.3</td>
<td>3.9</td>
<td>5.1</td>
<td>0.39</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>65.4</td>
<td>64.9</td>
<td>76.9</td>
<td>79.5</td>
<td>0.08</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>30.8</td>
<td>16.9</td>
<td>30.8</td>
<td>26.9</td>
<td>0.16</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>16.9</td>
<td>9.0</td>
<td>7.6</td>
<td>10.0</td>
<td>0.32</td>
</tr>
<tr>
<td>BMI</td>
<td>26.2 ± 4.0</td>
<td>26.8 ± 5.1</td>
<td>27.6 ± 5.1</td>
<td>30.3 ± 5.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>208.5 ± 34.9</td>
<td>215.6 ± 40.5</td>
<td>207.3 ± 39.5</td>
<td>209.9 ± 46.7</td>
<td>0.60</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>127.5 ± 31.7</td>
<td>133.4 ± 35.2</td>
<td>127.3 ± 32.0</td>
<td>128.6 ± 38.0</td>
<td>0.66</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>52.8 ± 15.8</td>
<td>54.7 ± 16.2</td>
<td>55.1 ± 14.5</td>
<td>53.1 ± 17.5</td>
<td>0.75</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>141.1 ± 60.4</td>
<td>135.9 ± 62.0</td>
<td>123.1 ± 48.7</td>
<td>137.9 ± 62.8</td>
<td>0.25</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>114.4 ± 35.1</td>
<td>108.6 ± 40.6</td>
<td>115.8 ± 42.3</td>
<td>126.3 ± 55.1</td>
<td>0.09</td>
</tr>
<tr>
<td>MMSE &lt;21 (%)</td>
<td>16.0</td>
<td>27.4</td>
<td>26.7</td>
<td>35.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Antihypertensive drugs (%)</td>
<td>68.8</td>
<td>70.3</td>
<td>80.5</td>
<td>85.5</td>
<td>0.04</td>
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<tr>
<td>Antiplatelet drugs (%)</td>
<td>41.6</td>
<td>46.0</td>
<td>63.6</td>
<td>63.2</td>
<td>0.007</td>
</tr>
<tr>
<td>Nitrates (%)</td>
<td>19.5</td>
<td>14.9</td>
<td>18.2</td>
<td>22.4</td>
<td>0.70</td>
</tr>
<tr>
<td>Statins (%)</td>
<td>22.1</td>
<td>14.9</td>
<td>14.3</td>
<td>19.7</td>
<td>0.53</td>
</tr>
<tr>
<td>Diuretics (%)</td>
<td>27.3</td>
<td>35.1</td>
<td>40.3</td>
<td>42.1</td>
<td>0.22</td>
</tr>
<tr>
<td>Beta-blockers (%)</td>
<td>10.4</td>
<td>8.1</td>
<td>10.4</td>
<td>11.8</td>
<td>0.90</td>
</tr>
<tr>
<td>Calcium channel blockers (%)</td>
<td>16.9</td>
<td>17.6</td>
<td>33.8</td>
<td>34.2</td>
<td>0.01</td>
</tr>
<tr>
<td>CEI inhibitors (%)</td>
<td>28.6</td>
<td>33.8</td>
<td>36.4</td>
<td>29.0</td>
<td>0.68</td>
</tr>
<tr>
<td>AT1 blockers (%)</td>
<td>31.2</td>
<td>31.1</td>
<td>28.6</td>
<td>43.4</td>
<td>0.21</td>
</tr>
<tr>
<td>LVMI (g/m².7)</td>
<td>44.5 ± 8.5</td>
<td>59.3 ± 4.1</td>
<td>72.1 ± 4.0</td>
<td>96.8 ± 16.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>65.1 ± 6.9</td>
<td>65.5 ± 8.9</td>
<td>63.2 ± 10.7</td>
<td>62.7 ± 9.5</td>
<td>0.18</td>
</tr>
<tr>
<td>PWV (m/s)</td>
<td>13.1 ± 3.2</td>
<td>13.0 ± 2.5</td>
<td>12.6 ± 2.6</td>
<td>12.9 ± 2.4</td>
<td>0.87</td>
</tr>
</tbody>
</table>

### Table 2: Determinants of dementia according to multivariable logistic regression

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.06</td>
<td>1.01–1.11</td>
<td>0.03</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.10</td>
<td>0.58–2.07</td>
<td>0.42</td>
</tr>
<tr>
<td>MBP</td>
<td>0.99</td>
<td>0.96–1.02</td>
<td>0.39</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td>0.84</td>
<td>0.43–1.62</td>
<td>0.42</td>
</tr>
<tr>
<td>LVMI 1st quartile</td>
<td>1.00</td>
<td>Reference</td>
<td>0.01</td>
</tr>
<tr>
<td>2nd quartile</td>
<td>1.75</td>
<td>0.76–4.29</td>
<td>0.39</td>
</tr>
<tr>
<td>3rd quartile</td>
<td>1.77</td>
<td>0.76–3.87</td>
<td>0.42</td>
</tr>
<tr>
<td>4th quartile</td>
<td>2.72</td>
<td>1.20–6.12</td>
<td>0.18</td>
</tr>
</tbody>
</table>

**Figure 1** Average cognitive function (mini-mental state examination score, left panel) and blood pressure levels (right panel) across quartiles of LVMI in the study population.
when body mass index, lipid, and glucose levels were added to the logistic model.

To investigate whether the observed inverse association between LVMI and global cognitive function was independent of arterial stiffness in a subgroup of 216 subjects, PWV was measured. This subgroup did not differ significantly in any parameter from the whole study population. The progressive deterioration of global cognitive function with increasing LVMI was confirmed in the subgroup of subjects with measured PWV (from the first to the fourth LVMI quartile, respectively: MMSE 25.0 ± 4.1, 24.3 ± 5.1, 23.7 ± 5.3, 21.9 ± 5.2; P < 0.01 by ANOVA). In multiple regression analysis model, including age, sex, hypertension, diabetes, traditional CV risk factors levels, and PWV (alternatively as continuous variable or categorized in quartiles) as covariates, LVMI persisted as a significant independent determinant of global cognitive function (β coefficient: −0.75, standard error 0.35, P < 0.05).

When carotid plaque was substituted to PWV or added to the multivariable logistic model including PWV also as covariate, LVMI persisted as a significant independent determinant of global cognitive function.

**Discussion**

In the present study, we observed that increasing LVMI is associated with poorer cognitive performance and higher likelihood of having dementia in older subjects and that such an association was independent of BP levels and/or large artery stiffness. In a small group of older subjects, LVMI has been reported to be associated with a 5-year decline in MMSE score. More recently, in the Framingham offspring, a similar association was confirmed. However, this association became not significant after adjustment for BP and other traditional CV risk factors levels.

The cross-sectional design of our study does not allow to elucidate pathophysiological pathways linking increasing LVM to decreasing cognitive performance in older subjects, independently of BP levels. One possible explanation for the observed association of LVMI and cognitive performance in older subjects, independent of BP levels, may be ascribed to the fact that LVMI may represent a sensitive indicator of lifelong exposure to higher BP levels. Alternatively, LVMI and specific LV geometric patterns have been found to be associated with cerebral white matter lesions, which in turn have been associated with cognitive decline in older subjects. Increased arterial stiffness might have represented another likely mechanism linking LVM with cognitive function. A greater arterial stiffness is known to increase LV afterload and, thus, favouring LV hypertrophy. Additionally, a close relationship between vascular and cardiac adaptation has been described. Of note, we recently reported, cross-sectionally and longitudinally, that increased arterial stiffness is a powerful determinant of cognitive decline in the elderly, independently of traditional CV risk factors levels. Nonetheless, our findings suggest that the association between increased LVM and poorer cognitive performance in older subjects is independent of arterial stiffness.

Our study has also potential implication for clinical management of older hypertensive subjects. In fact, it has extensively been debated whether lowering BP is the only goal of antihypertensive therapy or how BP is lowered matters. Our observation favours the idea that the way we lower BP is relevant in older subjects in order to preserve cognitive integrity and prevent disability. Clinical trial and observational studies clearly reported that not each and every antihypertensive drug is capable of reducing LVM for a similar reduction in BP levels.

The study has some limitations. First, the study population is constituted by health-seeking older subjects without acute events. Thus, our observations cannot be automatically transferred to the general older population. However, our study population may be representative of the typical older subject coming to medical attention and for whom a careful and appropriate prevention of functional disability—including that arising from cognitive decline—should be guaranteed.

Another limitation is represented by the lack of 24 h ambulatory blood pressure monitoring. A 24 h BP record is known to better correlate with LVMI and can provide further insight on the nocturnal BP levels, a strong independent determinant of LVMI and risk of cerebral vascular damage.

Future studies are welcome to disentangle the possible relationship between arterial stiffening, LVM, and cognitive decline in older subjects.

**Funding**

This study was partly supported by a grant of the Italian Ministry of Health Progetti di ricerca ex art. 56 legge n.289/2002 – Fondi anno 2005 - COM070027.

**Conflict of interest:** none declared.

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