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

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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 independency.[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 disease[10–12] 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

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damage is large artery stiffness, as measured by carotid–femoral pulse wave velocity (PWV).[15] Additionally, increased arterial stiffness has been associated with a higher LVM and risk of LV hypertrophy.[16,17] Of note, increased PWV has been found both cross-sectionally and longitudinally to be an independent significant determinant of cognitive performance in older subjects.[18,19]

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.[13,14] Left ventricular mass was estimated by the formula of Devereux *et al.*[20]: LVM (g) = 0.832 × [(LVID + IVS + PWT)3 − (LVIDd)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.[15]

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 automate device (Complior®, Artech-Medical, France), whose validation and reproducibility have been published previously.[18,19] 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.[21,22] 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.[7]

Statistical analysis

All analyses were performed via SPSS 8.0 for Windows. Data are presented as means ± SD, unless otherwise specified. χ^2 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

Table 1 Demographic and cardiovascular risk profile according to LVMI quartiles

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

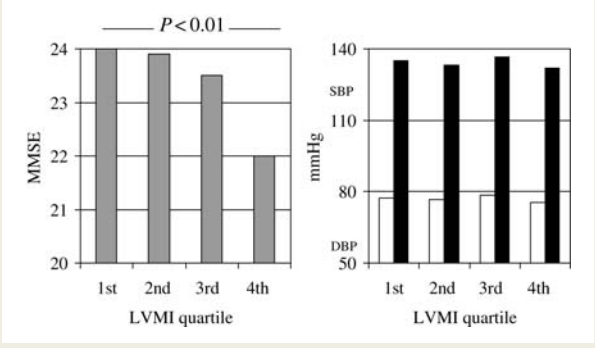

Figure 1 Average cognitive function (mini-mental state examination score, left panel) and blood pressure levels (right panel) across quartiles of LVMI in the study population.

Table 2 Determinants of dementia according to multivariable logistic regression

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

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 (χ^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

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 $\pm$ 4.1, 24.3 $\pm$ 5.1, 23.7 $\pm$ 5.3, 21.9 $\pm$ 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, LVM has been reported to be associated with a 5-year decline in MMSE score.[21] More recently, in the Framingham offspring, a similar association was confirmed.[22] However, this association became not significant after adjustment for BP and other traditional CV risk factors levels.[22]

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 LVM and cognitive performance in older subjects, independent of BP levels, may be ascribed to the fact that LVM may represent a sensitive indicator of lifelong exposure to higher BP levels.[23,24] Alternatively, LVM and specific LV geometric patterns have been found to be associated with cerebral white matter lesions,[25] which in turn have been associated with cognitive decline in older subjects.[26,27] 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.[28] Additionally, a close relationship between vascular and cardiac adaptation has been described.[29] Of note, we recently reported, cross-sectionally[18] and longitudinally,[19,30] 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.[15,31–33] 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.[34–36]

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[37] and can provide further insight on the nocturnal BP levels, a strong independent determinant of LVMI and risk of cerebral vascular damage.[38,39]

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

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Conflict of interest: none declared.

References

1. National High Blood Pressure Education Program Working Group. National High Blood Pressure Education Program Working Group report on hypertension in the elderly. *Hypertension* 1994;**23**:275–285.
2. Scuteri A, Najjar SS, Orru' M, Albai G, Strait J, Tarassov K, Piras MG, Cao A, Schlessinger D, Uda M, Lakatta EG. Age and gender specific awareness, treatment, and control of cardiovascular risk factors and subclinical vascular lesions in a founder population: the SardiNIA Study. *Nutr Metab Cardiov Dis* 2009; doi:10.1016/j.numecd.2008.11.004.
3. Agabiti-Rosei E, Muiesan ML. Hypertensive left ventricular hypertrophy: pathophysiological and clinical issues. *Blood Press* 2001;**10**:288–298.
4. Lauer MS, Anderson KM, Levy D. Influence of contemporary versus 30-year blood pressure levels on left ventricular mass and geometry: the Framingham Heart Study. *J Am Coll Cardiol* 1991;**18**:1287–1294.
5. Verdecchia P, Porcellati C, Reboldi G, Gattobigio R, Borgioni C, Pearson TA, Ambrosio G. Left ventricular hypertrophy as an independent predictor of acute cerebrovascular events in essential hypertension. *Circulation* 2001;**104**: 2039–2044.
6. Agabiti-Rosei E, Muiesan ML, Salvetti M. Evaluation of subclinical target organ damage for risk assessment and treatment in the hypertensive patients: left ventricular hypertrophy. *J Am Soc Nephrol* 2006;**17**(Suppl. 2):S104–S108.
7. Scuteri A, Palmieri L, Lo Noce C, Giampaoli S. Age-related changes in cognitive domains. A population-based study. *Aging Clin Exp Res* 2005;**17**:367–373.
8. Lobo A, Launer LJ, Fratiglioni L, Andersen K, Di Carlo A, Breteler MM, Copeland JR, Dartigues JF, Jagger C, Martinez-Lage J, Soininen H, Hofman A. Prevalence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. *Neurology* 2000;**54**(11 Suppl. 5):S4–S9.
9. Rocca WA, Hofman A, Brayne C, Breteler MM, Clarke M, Copeland JR, Dartigues JF, Engedal K, Hagnell O, Heeren TJ *et al.* The prevalence of vascular dementia in Europe: facts and fragments from 1980–1990 studies. EURODEM-Prevalence Research Group. *Ann Neurol* 1991;**30**:817–824.
10. Erkinjuntti T, Bowler JV, DeCarli CS, Fazekas F, Inzitari D, O'Brien JT, Pantoni L, Rockwood K, Scheltens P, Wahlund LO, Desmond DW. Imaging of static brain

lesions in vascular dementia: implications for clinical trials. *Alzheimer Dis Assoc Disord* 1999;**13**(Suppl. 3):S81–S90.
11. Esiri MM, Wilcock GK, Morris JH. Neuropathological assessment of the lesions of significance in vascular dementia. *J Neurol Neurosurg Psychiatry* 1997;**63**:749–753.
12. Pohjasvaara T, Mantyla R, Ylikoski R, Kaste M, Erkinjuntti T. Comparison of different clinical criteria (DSM-III, ADDTC, ICD-10, NINDS-AIREN, DSM-IV) for the diagnosis of vascular dementia. National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences. *Stroke* 2000;**31**:2952–2957.
13. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol* 2005;**4**:487–499.
14. Gorelick PB. Risk factors for vascular dementia and Alzheimer disease. *Stroke* 2004;**35**(11 Suppl. 1):2620.
15. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Boudier HA, Zanchetti A; ESH-ESC Task Force on the Management of Arterial Hypertension. 2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension: ESH-ESC Task Force on the Management of Arterial Hypertension. *J Hypertens* 2007;**25**:1751–1762.
16. Nichols WW, O'Rourke MF. Properties of the arterial wall: theory. In: Nichols WW, O'Rourke MF, eds. *McDonald's Blood Flow in Arteries*. 5th ed. London, United Kingdom: Hodder Arnold; 2005. p49–65.
17. Roman MJ, Ganau A, Saba PS, Pini R, Pickering TG, Devereux RB. Impact of arterial stiffening on left ventricular structure. *Hypertension* 2000;**36**:489–494.
18. Scuteri A, Brancati AM, Gianni W, Assisi A, Volpe M. Arterial stiffness is an independent risk factor for cognitive impairment in the elderly: a pilot study. *J Hypertens* 2005;**23**:1211–1216.
19. Scuteri A, Tesauro M, Appolloni S, Preziosi F, Brancati AM, Volpe M. Arterial stiffness as an independent predictor of longitudinal changes in cognitive function in the older individual. *J Hypertens* 2007;**25**:1035–1040.
20. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986;**57**:450–458.
21. Kähönen-Väre M, Brunni-Hakala S, Lindroos M, Pitkala K, Strandberg T, Tilvis R. Left ventricular hypertrophy and blood pressure as predictors of cognitive decline in old age. *Aging Clin Exp Res* 2004;**16**:147–152.
22. Elias MF, Sullivan LM, Elias PK, D'Agostino RB Sr, Wolf PA, Seshadri S, Au R, Benjamin EJ, Vasan RS. Left ventricular mass, blood pressure, and lowered cognitive performance in the Framingham offspring. *Hypertension* 2007;**49**:439–445.
23. Schillaci G, Verdecchia P, Porcellati C, Cuccurullo O, Cosco C, Perticone F. Continuous relation between left ventricular mass and cardiovascular risk in essential hypertension. *Hypertension* 2000;**35**:580–586.
24. Verdecchia P, Carini G, Circo A, Dovellini E, Govannini E, Lombardo M, Slinas P, Gorini M, Maggioni AP, and the MAVI Study Group. Left ventricular mass and cardiovascular morbidity in essential hypertension: the MAVI study. *J Am Coll Cardiol* 2001;**38**:1829–1835.
25. Selvetella G, Notte A, Maffei A, Calistri V, Scamardella V, Frati G, Trimarco B, Colonnese C, Lembo G. Left ventricular hypertrophy is associated with asymptomatic cerebral damage in hypertensive patients. *Stroke* 2003;**34**:1766–1770.
26. van Dijk EJ, Prins ND, Vrooman HA, Hofman A, Koudstaal PJ, Breteler MM. Progression of cerebral small vessel disease in relation to risk factors and cognitive consequences: Rotterdam Scan study. *Stroke* 2008;**39**:2712–2719.
27. Longstreth W, Manolio T, Arnold A, Burke G, Bryan N, Jungreis C, Enright P, O'Leary D, Fried L. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. *Stroke* 1996;**27**:1274–1282.
28. Najjar SS, Scuteri A, Lakatta EG. Arterial aging: is it an immutable cardiovascular risk factor? *Hypertension* 2005;**46**:454–462.
29. Muiesan ML, Salvetti M, Zulli R, Pasini GF, Bettoni G, Monteduro C, Rizzoni D, Castellano M, Agabiti-Rosei E. Structural association between the carotid artery and the left ventricle in a general population in Northern Italy: the Vobarno study. *J Hypertens* 1998;**16**:1805–1812.
30. Waldstein SR, Rice SC, Thayer JF, Najjar SS, Scuteri A, Zonderman AB. Pulse pressure and pulse wave velocity are related to cognitive decline in the Baltimore Longitudinal Study of Aging. *Hypertension* 2008;**51**:99–104.
31. Siragy HM. Evidence for benefits of angiotensin receptor blockade beyond blood pressure control. *Curr Hypertens Rep* 2008;**10**:261–267.
32. Blood Pressure Lowering Treatment Trialists' Collaboration, Turnbull F, Neal B, Ninomiya T, Algert C, Arima H, Barzi F, Bulpitt C, Chalmers J, Fagard R, Gleason A, Heritier S, Li N, Perkovic V, Woodward M, MacMahon S. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. *BMJ* 2008;**336**:1121–1123.
33. Scuteri A. Slowing arterial aging: how far have we progressed? *J Hypertens* 2007;**25**:509–510.
34. Ruilope LM, Schmieder RE. Left ventricular hypertrophy and clinical outcomes in hypertensive patients. *Am J Hypertens* 2008;**21**:500–508.
35. Muiesan ML, Salvetti M, Paini A, Monteduro C, Galbassini G, Bonzi B, Poisa P, Belotti E, Agabiti Rosei C, Rizzoni D, Castellano M, Agabiti Rosei E. Inappropriate left ventricular mass changes during treatment adversely affects cardiovascular prognosis in hypertensive patients. *Hypertension* 2007;**49**:1077–1083.
36. Kjeldsen SE, Dahlöf B, Devereux RB, Julius S, Aurup P, Edelman J, Beevers G de Faire U, Fyhrquist F, Ibsen H, Kristianson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Snapinn S, Wedel H; LIFE (Losartan Intervention for Endpoint Reduction) Study Group. Effects of losartan on cardiovascular morbidity and mortality in patients with isolated systolic hypertension and left ventricular hypertrophy: a Losartan Intervention for Endpoint Reduction (LIFE) substudy. *JAMA* 2002;**288**:1491–1498.
37. Parati G, Pomidossi G, Albini F, Malaspina D, Mancia G. Relationship of 24 h blood pressure mean and variability to severity of target organ damage in hypertension. *J Hypertens* 1987;**5**:93–98.
38. Mancia G, Bombelli M, Facchetti R, Madotto F, Corrao G, Trevano FQ, Grassi G, Sega R. Long-term prognostic value of blood pressure variability in the general population: results of the Pressioni Arteriose Monitorate e Loro Associazioni Study. *Hypertension* 2007;**49**:1265–1270.
39. Sander D, Winbeck K, Klingelhofer J, Conrad B. Extent of cerebral white matter lesions is related to changes of circadian blood pressure rhythmicity. *Arch Neurol* 2000;**57**:1302–1307.