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Correlations between left ventricular mass index and cerebrovascular lesion

Research Article

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Abstract: Left ventricular (LV) mass and LV geometry are well-established measures of hypertension chronicity and severity, have a prognostic value on cardiovascular morbidity and mortality, and are related to asymptomatic cerebral small-artery disease (SAD) and large-artery disease (LAD). The aim of the present study was to clarify the different effects of LV mass and LV geometry on underlying SAD compared with its effects on underlying LAD in ischemic stroke patients. Four hundred three ischemic stroke patients underwent echocardiography to determine LV mass index and relative wall thickness. Brain magnetic resonance imaging, angiography, and carotid magnetic resonance angiography were preformed to detect LAD (≥50% stenosis) and SAD (leukoaraiosis, microbleeds, and old lacunar infarction) in the brain. Multivariate analyses showed that the LV mass index was highly associated with underlying SAD but not with underlying LAD. Among the various subtypes of SAD, only cerebral microbleeds were closely related to the LV mass index. Concentric LV hypertrophy was not related to the presence of either SAD or LAD. Subgroup analyses revealed that, among the various subtypes of SAD, only cerebral microbleeds were associated with concentric LV hypertrophy. In conclusion, cerebral microbleeds may imply more advanced target organ damage than underlying LAD and ischemic subtypes of SAD.

Keywords: *Left ventricular mass index • Left ventricular geometry • Left ventricular hypertrophy • Magnetic resonance imaging • Stroke • Echocardiography • Cerebral microbleeds*

1. Introduction

Echocardiographic left ventricular (LV) mass is a well-established measure of hypertension chronicity and severity and an independent predictor of cardiovascular morbidity and mortality [1-5]. LV mass is associated with incident ischemic stroke [6] and asymptomatic cerebrovascular lesions [7-17]. In patients with LV hypertrophy, ischemic subtypes of cerebral small-artery disease (SAD), such as lacunar infarction [10,11] or leukoaraiosis [8,10], are frequent. Moreover, a close relationship has been reported between LV hypertrophy and cerebral microbleeds in hypertensive stroke patients [9]. In addition, LV mass is associated with large-artery disease (LAD), such as extracranial carotid artery disease [7,12-18].

There have been reports of incremental risk associated with abnormal LV geometry beyond a simple LV mass increase. From LV mass and relative wall thickness, 3 abnormal geometric patterns, i.e., concentric LV hypertrophy, eccentric LV hypertrophy, and concentric LV remodeling, are identified that appear to carry different risks for cardiovascular events [19]: concentric hypertrophy (increase in both LV mass and relative wall thickness) carries the highest risk, followed by eccentric hypertrophy (increased LV mass, normal relative wall thickness) [3,5]. In subjects with abnormal LV geometry, asymptomatic cerebral lesions are

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frequent [7-9,20]. Furthermore, abnormal LV geometry is associated with extracranial carotid artery disease [7].

However, it is not known whether LV mass and abnormal LV geometry are more closely associated with SAD or LAD. Because it is known that SAD is more highly associated with hypertension than is LAD [21], we hypothesized that LV mass and abnormal LV geometry might be more closely related to SAD than LAD. Therefore, our study was performed to clarify the different effects of LV mass and LV geometry on underlying cerebral SAD compared with its effects on underlying LAD in ischemic stroke patients.

2. Material and Methods

2.1. Patient selection

We retrospectively collected the records of ischemic stroke patients with an onset less than 7 days before presentation at Seoul National University Hospital from October 2002 to March 2006. Our study was approved by an independent ethic committee in Seoul National University Hospital (H-1006-134-322) and performed in compliance with the principles of the Declaration of Helsinki (1964). Four hundred three patients met the following inclusion criteria: 1) the availability of complete clinical and laboratory data, including height, body weight, serum cholesterol concentration, electrocardiography, and transthoracic echocardiography; 2) available medical history concerning hypertension, diabetes, smoking, a history of previous stroke, and antihypertensive and antithrombotic medication; 3) absence of cardiac disease (including congestive heart failure, previous myocardial infarction, and atrial fibrillation) with potential influence on echocardiographic variables [8,20]; and 4) artifact-free brain magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) and carotid MRA allowing for the evaluation of SAD and LAD.

Hypertension was considered present if a subject had repeated blood pressure readings above 140/90 mm Hg at intervals of ≥1 week or had a previous history of hypertension or antihypertensive medication. Diabetes was defined as a fasting serum glucose ≥126 mg/dL, a random glucose ≥200 mg/dL, a history of physician-diagnosed diabetes, use of insulin or an oral hypoglycemic agent. An active smoker was defined as a patient who used tobacco within one month of admission. Body mass index was calculated as weight (kg) divided by height (m) squared. Stroke etiology was classified according to the Trial of ORG 10172 in Acute Stroke Treatment criteria [22].

2.2. Echocardiographic studies

Transthoracic echocardiography was performed during a period of convalescence (usually between 7 and 14 days after ictus) using an Acuson 128XP/10c echocardiograph equipped with a V4c multihertz probe (Siemens, Munich, Germany). LV masses were estimated using the formula of Devereux and Reichek (Penn convention) [23]: LV mass (g) = 1.04 × ([LV internal dimension at diastole + interventricular septal thickness + posterior wall thickness]^3 - [LV internal dimension at diastole]^3) - 13.6. Calculated LV masses were divided by body surface areas to obtain LV mass indices. LV hypertrophy was defined as an LV mass index of >135 g/m^2 for men and >110 g/m^2 for women [9,24]. Relative wall thickness was calculated using the standard formula [25]: 2 × posterior wall thickness/LV internal dimension at diastole. Wall thickness was considered to be increased when relative wall thickness was >0.45 [9]. Based on LV morphology, subjects were classified into four groups: concentric LV hypertrophy (LV hypertrophy and increased relative wall thickness), eccentric LV hypertrophy (LV hypertrophy and normal relative wall thickness), concentric LV remodeling (normal LV mass and increased relative wall thickness), and normal geometry (normal LV mass and normal relative wall thickness) [9,26].

Transesophageal echocardiography was performed in selected patients when there was a need to assess the right and left atrial cavities or the thoracic aorta.

2.3. MRI

Brain MRI (axial T2-weighted spin-echo, fluid-attenuated inversion recovery, and axial T2*-weighted gradient echo sequence) and brain and carotid MRA were obtained as described in our previous studies [9,21]. MRI and MRA were performed at 1.5T in ≈90% of the patients and at 3T in the other patients.

The presence of underlying LAD (extracranial carotid or intracranial arterial stenosis ≥50%) and of underlying SAD (old lacunar infarction, cerebral microbleeds, or leukoaraiosis) was assessed as described in our previous studies [9,21,27]. Cerebral microbleeds were defined as round hypointense lesions of diameter ≤5 mm by gradient echo sequence imaging [9,21]. Old lacunar infarction was defined as a focal lesion of ≤3 mm and ≤20 mm in diameter with the signal intensity of cerebrospinal fluid [21]. Leukoaraiosis was defined as areas of high signal intensity in the T2-weighted sequences that were located at the periventricular white matter or the centrum semiovale [27,28]. The severity of leukoaraiosis was graded according to the criteria

Table 1. Baseline characteristics of 403 patients.

Characteristic	n (%) or mean±SD
Male	277 (68.7)
Age (years)	63±12
Body mass index (kg/m^2)	24.3±2.9
Hypertension	271 (67.2)
Diabetes	136 (33.7)
Total cholesterol (mg/dL)	182±38
HDL cholesterol (mg/dL)	43±13
Smokers	95 (23.6)
Previous stroke	86 (21.3)
Previous antihypertensive medication	170 (42.2)
Previous antiplatelet medication	58 (14.4)
Stroke subtype	
Large artery atherosclerosis	135 (33.5)
Small vessel occlusion	166 (41.2)
Cardioembolism	18 (4.5)
Others	6 (1.5)
Undetermined	78 (19.4)
LV mass index (g/m^2)	131.0±37.3
LV relative wall thickness	0.44±0.09
LV geometry	
Normal	152 (37.7)
Concentric remodeling	53 (13.2)
Eccentric hypertrophy	104 (25.8)
Concentric hypertrophy	94 (23.3)
Large-artery disease	49 (12.2)
Small-artery disease	285 (70.7)
Cerebral microbleeds	123 (30.5)
Old lacunar infarction	104 (25.8)
Leukoaraiosis	258 (64.0)
Grade 0	145 (36.0)
Grade 1	131 (32.5)
Grade 2	83 (20.6)
Grade 3	44 (10.9)

SD: standard deviation; HDL: high-density lipoprotein; LV:left ventricle.

reported by Fazekas et al. as follows: absent (grade 0), punctuate foci (grade 1), beginning confluence of foci (grade 2) or large confluent areas (grade 3) [28].

2.4. Statistical analysis

Differences between the frequency distributions of categorical variables were analyzed using the chi-square test or Fisher's exact test. Differences between the continuous variables were evaluated by the Student's t-test or Kruskal-Wallis test followed by Mann-Whitney tests. A Bonferroni correction for multiple comparisons was applied when necessary. Variables whose p values were <0.15 were selected as potential adjusting variables. Then, 2 separate multivariate logistic regression models were constructed. Model 1 was used to examine the relations of LV mass index and relative wall thickness as continuous independent variables to 5 dichotomous dependent variables (LAD, SAD, and three subtypes of SAD), respectively. Model 2 was used to examine the relations of LV geometry as categorical independent variables to 5 dichotomous dependent variables (LAD, SAD, and three subtypes of SAD), respectively. LV mass index and LV geometry were analyzed separately because of their colinearity. Probabilities of <0.05 were considered significant. All statistical analyses were performed using SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Clinical characteristics of the ischemic stroke patients

A total of 403 ischemic stroke patients were included in this study. The patients were 277 men and 126 women; their mean age was 63±12 years. Two hundred seventy-one patients (67.2%) were hypertensive. LAD was present in 49 patients (12.2%), while SAD (old lacunar infarction, cerebral microbleeds, or leukoaraiosis) was present in 285 (70.7%). Cerebral microbleeds were present in 123 (30.5%) of the 403 patients, old lacunar infarction in 104 (25.8%), and leukoaraiosis in 258 (64.0%) (Table 1). Eighty (19.9%) of the 403 patients had cerebral microbleeds in the cortical-subcortical region, 82 patients (20.3%) in the central gray matter (basal ganglia and thalamus), and 55 patients (13.6%) in the infratentorial area (brainstem and cerebellum).

3.2. LV mass index and cerebrovascular lesions

First, we investigated the relation of clinical characteristics to LAD and SAD. In univariate analyses, age, and the prevalence of diabetes were significantly higher in patients with LAD than in patients without LAD (Table 2). Compared with patients without SAD, patients with SAD were more likely to be older, female, hypertensive, and taking antihypertensive medications, and also to have a higher LV mass index and LV relative wall thickness and higher frequency of previous stroke (Table 2).

Second, we examined the associations between clinical characteristics and the various SAD subtypes. In univariate analyses, age, LV mass index, LV relative wall thickness, the prevalence of hypertension, previous

Table 2. Clinical characteristics of 403 patients according to the presence of large-artery disease (LAD) and small-artery disease (SAD).

Characteristic	No LAD (n = 354)	LAD (n = 49)	p-value			No SAD (n = 118)	SAD (n = 285)	p-value		
			Univariate	Multivariate				Univariate	Multivariate	
	n (%) or mean±SD	n (%) or mean±SD		Model 1	Model 2	n (%) or mean±SD	n (%) or mean±SD		Model 1	Model 2
Male	240 (67.8)	37 (75.5)	0.275			91 (77.1)	186 (65.3)	0.019*	0.049*	0.27
Age (years)	63±11	67±11	0.01*	0.023*	0.03*	57±13	66±10	<0.001‡	<0.001‡	<0.001‡
Body mass index (kg/m^2)	24.4±2.9	24.3±2.7	0.952			24.4±3.1	24.3±2.7	0.831		
Hypertension	237 (66.9)	36 (69.4)	0.733			53 (44.9)	218 (76.5)	<0.001‡	0.001†	0.001†
Diabetes	112 (31.6)	24 (49.0)	0.016*	0.038*	0.039*	38 (32.2)	98 (34.4)	0.673		
Total cholesterol (mg/dL)	183±39	178±37	0.413			181±36	183±39	0.674		
HDL cholesterol (mg/dL)	43±13	41±12	0.199			43±12	43±13	0.86		
Smokers	80 (22.6)	15 (30.6)	0.215			31 (26.3)	64 (22.5)	0.412		
Previous stroke	72 (20.3)	14 (28.6)	0.187			14 (11.9)	72 (25.3)	0.003†	0.02*	0.017*
Previous antihypertensive medication	144 (40.7)	26 (53.1)	0.1	0.49	0.435	29 (24.6)	141 (49.5)	<0.001‡	0.946	0.925
Previous antiplatelet medication	50 (14.1)	8 (16.3)	0.681			15 (12.7)	43 (15.1)	0.536		
LV mass index (g/m^2)	129.9±37.2	138.8±37.6	0.118	0.216		119.9±33.3	135.6±37.9	<0.001‡	0.014*	
LV relative wall thickness	0.44±0.09	0.44±0.10	0.56	0.617		0.42±0.08	0.45±0.09	0.007†	0.739	
Concentric LV hypertrophy	80 (22.6)	14 (28.6)	0.369		0.776	17 (14.4)	77 (27.0)	0.006†		0.275

Model 1 was used to examine the relations of LV mass index and relative wall thickness as continuous independent variables to dichotomous dependent variables. Model 2 was used to examine the relation of LV geometry as a categorical independent variable to dichotomous dependent variables. LV mass index and LV geometry were analyzed separately because of their colinearity. Variables were selected for entry into the multivariate models based on the results of univariate analyses (p<0.15).

**p<0.05, †p<0.01, ‡p<0.001.*

LAD- large-artery disease, SAD- small-artery disease, SD- standard deviation, HDL- high-density lipoprotein, LV- left ventricle.

Table 3. Clinical characteristics of 403 patients according to the presence of cerebral microbleeds.

Characteristic	No cerebral microbleeds (n = 280)	Cerebral microbleeds (n = 123)	p-value		
			Univariate	Multivariate	
	n (%) or mean±SD	n (%) or mean±SD		Model 1	Model 2
Male	199 (71.1)	78 (63.4)	0.127	0.33	0.658
Age (years)	62±12	66±10	<0.001‡	0.108	0.101
Body mass index (kg/m^2)	24.3±2.9	24.4±2.8	0.842		
Hypertension	171 (61.1)	100 (81.3)	<0.001‡	0.028*	0.032*
Diabetes	97 (34.6)	39 (31.7)	0.566		
Total cholesterol (mg/dL)	184±39	179±38	0.194		
HDL cholesterol (mg/dL)	43±13	43±13	0.839		
Smokers	74 (26.4)	21 (17.1)	0.042*	0.182	0.16
Previous stroke	52 (18.6)	34 (27.6)	0.041*	0.109	0.083
Previous antihypertensive medication	104 (37.1)	66 (53.7)	0.002†	0.813	0.557
Previous antiplatelet medication	40 (14.3)	18 (14.6)	0.927		
LV mass index (g/m^2)	127.2±34.6	139.8±41.7	0.002†	0.046*	
LV relative wall thickness	0.43±0.08	0.46±0.10	0.007†	0.462	
Concentric LV hypertrophy	52 (18.6)	42 (34.1)	0.001†		0.015*

Model 1 was used to examine the relations of LV mass index and relative wall thickness as continuous independent variables to a dichotomous dependent variable. Model 2 was used to examine the relation of LV geometry as a categorical independent variable to a dichotomous dependent variable. LV mass index and LV geometry were analyzed separately because of their colinearity. Variables were selected for entry into the multivariate models based on the results of univariate analyses (p<0.15).
**p<0.05, †p<0.01, ‡p<0.001.*
SD- standard deviation, HDL- high-density lipoprotein, LV- left ventricle.

Table 4. Clinical characteristics of 403 patients according to the presence of leukoaraiosis.

Characteristic	No leukoaraiosis (n = 145)	Leukoaraiosis (n = 258)	p-value		
			Univariate	Multivariate	
	n (%) or mean±SD	n (%) or mean±SD		Model 1	Model 2
Male	110 (75.9)	167 (64.7)	0.021*	0.098	0.273
Age (years)	58±12	66±10	<0.001‡	<0.001‡	<0.001‡
Body mass index (kg/m^2)	24.3±3.0	24.4±2.7	0.896		
Hypertension	72 (49.7)	199 (77.1)	<0.001‡	0.003†	0.003†
Diabetes	50 (34.5)	86 (33.3)	0.815		
Total cholesterol (mg/dL)	181±41	183±37	0.532		
HDL cholesterol (mg/dL)	43±12	44±13	0.52		
Smokers	40 (27.6)	55 (19.8)	0.273		
Previous stroke	22 (15.2)	64 (24.8)	0.023*	0.143	0.129
Previous antihypertensive medication	39 (26.9)	131 (50.8)	<0.001‡	0.552	0.664
Previous antiplatelet medication	20 (13.8)	38 (14.7)	0.797		
LV mass index (g/m^2)	126.0±40.4	133.8±35.2	0.043*	0.507	
LV relative wall thickness	0.42±0.08	0.44±0.09	0.09	0.549	
Concentric LV hypertrophy	27 (18.6)	67 (26.0)	0.111		0.935

Model 1 was used to examine the relations of LV mass index and relative wall thickness as continuous independent variables to a dichotomous dependent variable. Model 2 was used to examine the relation of LV geometry as a categorical independent variable to a dichotomous dependent variable. LV mass index and LV geometry were analyzed separately because of their colinearity. Variables were selected for entry into the multivariate models based on the results of univariate analyses (p<0.15).
**p<0.05, †p<0.01, ‡p<0.001.*
SD- standard deviation, HDL- high-density lipoprotein, LV- left ventricle.

Table 5. Clinical characteristics of 403 patients according to the presence of old lacunar infarction.

Characteristic	No old lacunar infarction (n = 299)	Old lacunar infarction (n = 104)	p-value		
			Univariate	Multivariate	
	n (%) or mean±SD	n (%) or mean±SD		Model 1	Model 2
Male	199 (66.6)	78 (75.0)	0.11	0.157	0.135
Age (years)	63±12	64±10	0.52		
Body mass index (kg/m^2)	24.3±2.9	24.6±2.8	0.299		
Hypertension	183 (61.2)	88 (84.6)	<0.001‡	<0.001‡	<0.001‡
Diabetes	97 (32.4)	39 (37.5)	0.347		
Total cholesterol (mg/dL)	183±37	180±43	0.467		
HDL cholesterol (mg/dL)	44±13	41±11	0.084	0.215	0.189
Smokers	70 (23.4)	25 (24.0)	0.897		
Previous stroke	47 (15.7)	39 (37.5)	<0.001‡	0.002†	0.002†
Previous antihypertensive medication	115 (38.5)	55 (52.9)	0.01*	0.45	0.613
Previous antiplatelet medication	33 (11.0)	25 (24.0)	0.001†	0.63	0.685
LV mass index (g/m^2)	128.8±35.3	137.3±42.1	0.044*	0.307	
LV relative wall thickness	0.43±0.09	0.45±0.08	0.093	0.897	
Concentric LV hypertrophy	65 (21.7)	29 (27.9)	0.226		0.699

Model 1 was used to examine the relations of LV mass index and relative wall thickness as continuous independent variables to a dichotomous dependent variable. Model 2 was used to examine the relation of LV geometry as a categorical independent variable to a dichotomous dependent variable. LV mass index and LV geometry were analyzed separately because of their colinearity. Variables were selected for entry into the multivariate models based on the results of univariate analyses (p<0.15).
**p<0.05, †p<0.01, ‡p<0.001.*
SD:- standard deviation.;HDL- high-density lipoprotein; LV: left ventricle.

stroke, and the prior use of antihypertensive medication were significantly higher in patients with cerebral microbleeds than patients without cerebral microbleeds. The prevalence of smoking was significantly lower in patients with cerebral microbleeds than in the patients without (Table 3). Age, LV mass index, the prevalence of hypertension and previous stroke, and the prior use of antihypertensive medication were significantly higher in patients with leukoaraiosis than in patients without leukoaraiosis. The frequency of male sex was significantly lower in patients with leukoaraiosis than in patients without leukoaraiosis (Table 4). LV mass index, the prevalence of hypertension, previous stroke, and the prior use of antihypertensive medication and antithrombotic medication were significantly higher in patients with old lacunar infarction than in patients without old lacunar infarction (Table 5).

Finally, multivariate regression analyses were performed to obtain independent risks associated with each variable analyzed. The multivariate regression analyses demonstrated that old age was associated with both LAD [odds ratio (OR) per 10 years, 1.44; 95% confidence interval (CI), 1.05–1.95] and SAD [OR per 10 years, 1.79; 95% CI, 1.42–2.26] (Tables 2). Among the three subtypes of SAD, only leukoaraiosis was closely associated with old age (OR per 10 years, 1.84; 95% CI, 1.47–2.30) (Tables 3-5). Female sex was associated with SAD (OR, 1.75; 95% CI, 1.00–3.05) and diabetes was associated with LAD (OR, 1.93; 95% CI, 1.04–3.58). A history of previous stroke was associated with increased risk of SAD (OR, 2.23; 95% CI, 1.13–4.40) (Tables 2). Among the three subtypes of SAD, only old lacunar infarction was positively associated with a history of previous stroke (OR, 2.87; 95% CI, 1.45–5.65) (Tables 3-5). The presence of hypertension was significantly related to SAD (OR, 2.82; 95% CI, 1.51–5.28), but not LAD (Tables 2). All subtypes of SAD were highly related to hypertension: the ORs for cerebral microbleeds, leukoaraiosis, and old lacunar infarction were 2.03 (95% CI, 1.08–3.82), 2.46 (95% CI, 1.36–4.42), and 3.72 (95% CI, 1.85–7.49), respectively (Tables 3-5). Increasing LV mass index was associated with increased risk of SAD (OR per 30g/m^2, 1.35; 95% CI, 1.06–1.71), but not that of LAD (Tables 2). Among the three subtypes of SAD, only cerebral microbleeds were positively associated with LV mass index (OR per 30g/m^2, 1.23; 95% CI, 1.00–1.47) (Tables 3-5).

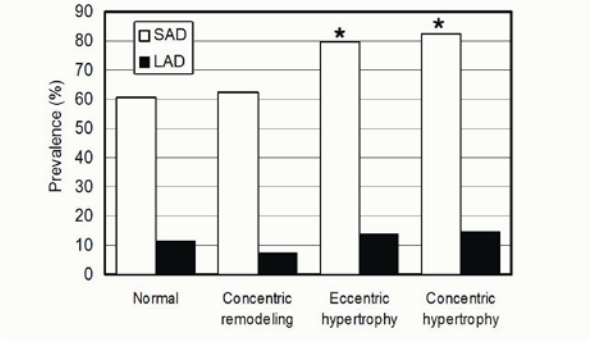
To evaluate an association between LV mass index and advanced leukoaraiosis, grade 2 and 3 leukoaraiosis were classified as advanced leukoaraiosis [21]. Advanced leukoaraiosis was significantly associated with age (OR per 10 years, 2.04; 95% CI, 1.58–2.67) and hypertension (OR, 2.42; 95% CI, 1.25–4.66), but not with LV mass index.

Table 6. Clinical characteristics of patients with each combination of subtypes of small-artery disease.

Characteristic	Group A (n=118) n (%) or mean±SD	Group B (n=162) n (%) or mean±SD	Group C (n=14) n (%) or mean±SD	Group D (n=109) n (%) or mean±SD	p-value
Male	91 (77.1)	108 (66.7)	9 (64.3)	69 (63.3)	0.121
Age (years)	57±13	66±10*	63±12	66±9*	<0.001
Body mass index (kg/m^2)	24.4±3.1	24.3±2.7	24.0±3.4	24.5±2.7	0.916
Hypertension	53 (44.9)	118 (72.8)*	10 (71.4)	90 (82.6)*	<0.001
Diabetes	80 (67.8)	103 (63.6)	9 (64.3)	75 (68.8)	0.805
Total cholesterol (mg/dL)	181±36	186±40	172±33	179±39	0.461
HDL cholesterol (mg/dL)	43±12	43±13	40±6	44±14	0.899
Smokers	31 (26.3)	43 (26.5)	2 (14.3)	19 (17.4)	0.238
Previous stroke	14 (11.9)	38 (23.5)	3 (21.4)	31 (28.4)*	0.018
Previous antihypertensive medication	89 (75.4)	87 (53.7)*	9 (64.3)	48 (44)*	<0.001
Previous antiplatelet medication	103 (87.3)	137 (84.6)	11 (78.6)	94 (86.2)	0.799
LV mass index (g/m^2)	119.9±33.3	132.4±34.6*	142.2±31.2*	139.4±43.0*	<0.001
LV relative wall thickness	0.42±0.08	0.44±0.09	0.46±0.11	0.45±0.10*	0.047

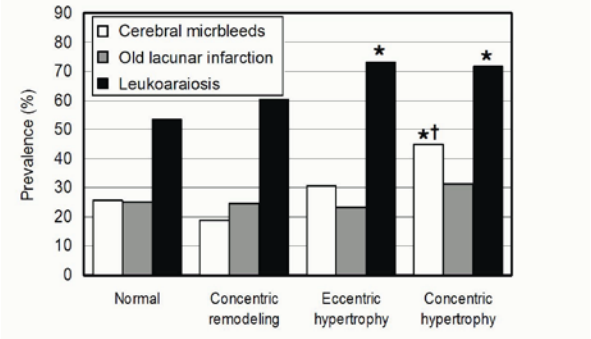
Group A- patients without either cerebral microbleeds or ischemic small-artery disease, group B- patients with ischemic small-artery disease but without cerebral microbleeds, group C- patients with cerebral microbleeds but without ischemic small-artery disease, group D- patients with coexistence of cerebral microbleeds and ischemic small-artery disease. For the comparison test among the four groups, the nonadjusted statistical level of significance of p<0.05 corresponds to a Bonferroni adjusted statistical significance of p<0.0083.
**p<0.0083 vs. group A.*
SD: standard deviation; HDL: high-density lipoprotein; LV: left ventricle.

Figure 1. Percentage of small-artery disease (SAD) and large-artery disease (LAD) according to left ventricular geometry.



For the comparison test among the four groups of left ventricular geometry, the nonadjusted statistical level of significance of p<0.05 corresponds to a Bonferroni adjusted statistical significance of p<0.0083.
**p<0.0083 vs. normal geometry, †p<0.0083 vs. concentric remodeling.*

Figure 2. Percentage of various types of small-artery disease according to left ventricular geometry.



For the comparison test among the four groups of left ventricular geometry, the nonadjusted statistical level of significance of p<0.05 corresponds to a Bonferroni adjusted statistical significance of p<0.0083.
**p<0.0083 vs. normal geometry, †p<0.0083 vs. concentric remodeling.*

3.3. LV geometry and cerebrovascular lesions

In univariate analyses, the prevalence of SAD was significantly higher in the eccentric LV hypertrophy and concentric LV hypertrophy groups than in the normal geometry group, whereas the prevalence of LAD was similar in the four groups (Figure 1). The prevalence of cerebral microbleeds was higher in the concentric LV hypertrophy group than in the normal geometry and concentric LV remodeling groups. The prevalence of leukoaraiosis was significantly higher in the eccentric LV hypertrophy and concentric hypertrophy groups than in the normal geometry group. The prevalence of old lacunar infarction was similar in the four groups (Figure 2).

Next, the LV geometric pattern was dichotomized into concentric LV hypertrophy or other geometric patterns. In univariate analysis, the prevalences of SAD and cerebral microbleeds were higher in patients with concentric LV hypertrophy than in patients without concentric LV hypertrophy (Table 2 and 3). The multivariate regression analyses demonstrated that concentric LV hypertrophy was not associated with the presence of either SAD or LAD (Table 2). Subgroup analyses revealed that among the three subtypes of SAD, only cerebral microbleeds were associated with abnormal LV geometry, especially concentric LV hypertrophy (OR, 1.85; 95% CI, 1.23–3.05) (Table 3).

3.4. Combinations of the presence or absence of cerebral microbleeds and ischemic SAD

Patients were divided into 4 groups by the presence or absence of cerebral microbleeds and ischemic SAD as follows: group A, patients without either cerebral microbleeds or ischemic SAD; group B, patients with ischemic SAD but without cerebral microbleeds; group C, patients with cerebral microbleeds but without ischemic SAD; and group D, patients with coexistence of cerebral microbleeds and ischemic SAD. Compared with patients in group A, patients in group B and D were more likely to be older, hypertensive, and taking antihypertensive medications. Compared with patients in group A, patients in group B, C, and D were more likely to have a higher LV mass index. Compared with patients in group A, patients in group D were more likely to have a higher LV relative wall thickness and a higher frequency of previous stroke (Table 6).

4. Discussion

The observation that LV mass may affect the risk of asymptomatic cerebrovascular lesions has precedents in the literature [7-14]. Several studies have shown associations between asymptomatic ischemic subtypes of SAD and LV mass in hypertensive patients without a stroke history [8,10,11]. In addition, in our previous study, which included hypertensive stroke patients, we found that LV mass is correlated with the grade of cerebral microbleeds [9]. Furthermore, LV mass is closely associated with carotid intima-media thickness and the presence of carotid plaque [7,12-18].

In our previous study, SAD demonstrated strong associations with hypertension, whereas LAD was associated with diabetes but not with hypertension [21]. LV hypertrophy is likely to occur secondary to hypertension [2], so we anticipated that SAD, rather than LAD, might be more closely related to LV mass. In agreement with our hypothesis, we found that SAD is associated with LV mass, but that LAD is not. However, contrary to our hypothesis, our regression analyses showed that the ischemic subtypes of SAD (old lacunar infarction and leukoaraiosis) are not associated with LV mass, although the ischemic subtypes of SAD were associated with hypertension. Thus, factors other than the simple presence of hypertension affect the associations between LV mass and cerebral microbleeds.

Although lacunar infarction, leukoaraiosis, and cerebral microbleeds are thought to be signs of underlying microangiopathy, their pathogenic mechanisms may differ slightly [9,29]. The reason that some individuals with similar risk factors develop leukoaraiosis whereas others develop cerebral microbleeds is unknown. The concept of hypertensive burden measured in the form of LV mass may be an answer to this question. LV mass has been reported to be correlated with the severity of hypertensive retinopathy and renal involvement [1]. Since LV mass is a well established measure of the chronicity and severity of hypertension, cerebral microbleeds may indicate more advanced target organ damage caused by hypertension than may ischemic subtypes of SAD [1,2]. In accordance with our results, Japanese investigators reported that LV mass is higher in patients with symptomatic hemorrhagic stroke than in those with symptomatic ischemic stroke [30].

The value of LV geometry in the prediction of cerebrovascular disease has been only minimally investigated [8,20,31]. Concentric hypertrophy carries the greatest ischemic stroke risk, followed by eccentric hypertrophy [31]. Concentric remodeling carries a slightly increased stroke risk [31]. Hypertensive patients with concentric LV hypertrophy display more pronounced asymptomatic ischemic cerebral lesions compared with patients with eccentric LV hypertrophy [20]. Concentric LV hypertrophy is reported to be associated with leukoaraiosis in asymptomatic middle-aged hypertensive patients [8]. Furthermore, abnormal LV geometry is associated with extracranial carotid artery disease [7]. A stepwise increase in carotid intima-media thickness occurs from the lowest values in subjects with normal LV geometry to intermediate in those with concentric LV remodelling and eccentric LV hypertrophy and to the highest level in subjects with concentric LV hypertrophy [7]. Patients with concentric LV remodelling and concentric LV hypertrophy have a significantly greater relative carotid wall thickness than those with normal LV geometry and eccentric LV hypertrophy [7]. These suggest that LV geometry may contribute to cerebrovascular lesions in ways not necessarily related to LV mass. Our study shows that concentric LV hypertrophy is correlated with the presence of only cerebral microbleeds among three subtypes of SAD. Hypertensive patients with concentric LV hypertrophy have more advanced target organ damage, such as renal and retinal involvement, than those with other LV geometry [1,32]. This relationship strengthens our belief that cerebral microbleeds imply more advanced target organ damage than does ischemic SAD.

Hypertension was the most consistent risk factor for cerebral microbleeds in previous studies [33]. Age, history of previous stroke, antiplatelet medications, low total serum cholesterol and high HDL-cholesterol concentrations, and LV mass index were also

associated with a high prevalence or number of cerebral microbleeds in previous studies [34,35]. In univariate analyses of our results, age, hypertension, LV mass index, and history of previous stroke were significantly associated with the prevalence of cerebral microbleeds. In multivariate analyses, however, only hypertension and LV mass index remained significant, confirming the fact that hypertension is the most important risk factor for cerebral microbleeds.

Cerebral microbleeds were present in 30.5% of our patients with ischemic stroke. A recent systemic review reported that the prevalence of cerebral microbleeds is 5% in healthy adults, 34% in people with ischemic stroke, and 60% in people with spontaneous intracerebral hemorrhage [33]. Previous distribution analyses of cerebral microbleeds have cast light on the pathogenesis of cerebral microbleeds [9,36]. Sun *et al*. have shown that the location of cerebral microbleeds in patients without hypertension was limited to the cortical-subcortical region in 40.3% compared to 20.4% of those with hypertension [36]. Their patients with hypertension had higher frequencies of distribution in the central gray matter (26.1% vs. 17.7%) and the infratentorial region (8.1% vs. 6.5%) than those without hypertension [36]. Previously, we have reported data correlating LV mass index and the presence of microbleeds in precisely the locations seen in patients with hypertensive vasculopathy: the central gray and infratentorial regions [9]. No positive regional relationship was observed in the subcortical white matter [9]. These findings may be related to the epidemiologic data that intracerebral hemorrhages in the basal ganglia or thalamus are generally caused by chronic hypertension and that lobar hemorrhage is caused by various diseases such as cerebral amyloid angiopathy and vascular anomalies [37,38]. In patients with hypertension, cerebral microbleeds are thought to be due to lipohyalinosis, microatheromas, or Charcot-Bouchard microaneurysms [36]. These predisposing events are primarily found in perforating arteries and deep brain regions including the basal ganglia and thalamus, which, incidentally, are the most frequent locations of cerebral microbleeds in patients with hypertension [36]. The microbleeds burden in the deep gray and infratentorial brain regions may reflect disease chronicity and severity [9].

There are some limitations to our study. First, we studied underlying SAD and LAD but not acute ischemic stroke mechanisms. We mainly focused on silent lesions in rating cerebral SAD, so we excluded newly developed lacunar infarctions from cerebral SAD. The implication of studying underlying SAD and LAD is obvious since the underlying SAD and LAD are regarded as surrogate markers for future stroke subtypes [39]. Second, LV mass index is only indirect evidence of chronicity and severity of hypertension. We did not collect the data concerning the duration of hypertension in our patients. Third, the imaging modalities varied in our study population; MRI and MRA were performed at 1.5T in ~90% of the patients and at 3T in ~10%. Another limitation is that our results apply only to ischemic stroke patients. We might extrapolate to a population at high risk for developing stroke, but would be cautious about generalizing to a general population.

In conclusion, in ischemic stroke patients, cerebral microbleeds were closely associated with the LV mass index and concentric LV hypertrophy, while underlying LAD and ischemic subtypes of SAD (old lacunar infarction and leukoaraiosis) were not. Cerebral microbleeds may indicate more advanced target organ damage than LAD and ischemic subtypes of SAD.

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