Journal of Cerebrovascular and Endovascular Neurosurgery
ISSN 2234-8565, EISSN 2287-3139, http://dx.doi.org/10.7461/jcen.2013.15.3.131

Clinical Article

Relation Between Left Atrial Enlargement and Stroke Subtypes in Acute Ischemic Stroke Patients

Hye-Young Shin[1], In-Hye Jeong[1], Chang-Ki Kang[2], Dong-Jin Shin[1], Hyeon-Mi Park[1], Kee-Hyung Park[1], Young-Hee Sung[1], Dong-Hoon Shin[1], Young Noh[1], Yeong-Bae Lee[1]

[1]*Department of Neurology, Gachon University Gil Medical Center, Incheon, Korea*
[2]*Neuroscience Research Institute, Gachon University of Medicine and Science, Incheon, Korea*

Objective : Increased atrial size is frequently seen in ischemic stroke patients in clinical practice. There is controversy about whether left atrial enlargement (LAE) should be regarded as a risk factor for cerebral infarction. We investigated the association between indexed left atrial volume (LAVI) and conventional stroke risk factors as well as stroke subtypes in acute ischemic stroke patients.

Methods : One hundred eighty two acute cerebral infarction patients were included in this study. Brain magnetic resonance imaging and transthoracic echocardiography were done for all patients within 30 days of diagnosis of acute cerebral infarction. Echocardiographic LAE was identified when LAVI was more than 27 mL/m^2. Stroke subtypes were classified by the Trial of Org 10171 in acute stroke treatment classification.

Results : There were significant differences between subjects with normal and increased LAVI in prevalence of stroke risk factors including atrial fibrillation (p = 0.001), hypertension (p = 0.000), valvular heart disease (p = 0.011) and previous stroke (p = 0.031). An increased LAVI was associated with cardioembolic subtype with an adjusted odds ratio was 6.749 (p = 0.002) compared with small vessel disease.

Conclusion : Increased LAVI was more prevalent in those who had cardiovascular risk factors, such as atrial fibrillation, hypertension, valvular heart disease and history of previous stroke. LAE influenced most patients in all subtypes of ischemic stroke but was most prevalent in the cardioembolic stroke subtype. Increased LAVI might be a risk factor of cerebral infarction, especially in patients with cardioembolic stroke subtype.

Keywords Left atrial enlargement, Ischemic stroke, Stroke subtype, Echocardiography

J Cerebrovasc Endovasc Neurosurg. 2013 September;15(3):131-136
Received : 21 March 2013
Revised : 18 June 2013
Accepted : 16 July 2013

Correspondence to Yeong-Bae Lee
Department of Neurology, Gachon University Gil Medical Center, 1198, Guwol-dong, Namdong-gu, Incheon 405-760, Korea

Tel : 82-32-460-3346
Fax : 82-32-460-3344
E-mail : lyb@gilhospital.com

Funding sources of this article are from Gachon University Gil Medical Center.
Portions of this work were presented in poster form as 31th Annual meeting of the Korean Neurological Association, Busan, Korea, October 6, 2011.

INTRODUCTION

Stroke is the second leading cause of death in Korea and is associated with severe disability and mortality.[17] The identification and treatment of stroke risk factors has important consequences on the prognosis of stroke.[4)7)] Well-known definite risk factors for ischemic stroke include dyslipidemia, hypertension, diabetes mellitus, ischemic heart disease, atrial fibrillation, valvular heart disease, carotid stenosis, cigarette smoking, and obesity. We have frequently seen ischemic stroke patients with left atrial enlargement (LAE) in clinical practice. This condition indicates increased left ventricle (LV) filling pressure and the subsequent remod-

eling process in hypertensive heart disease.[3] In the past few years, LAE has been found to be a risk factor for cardiovascular disease, atrial fibrillation, systemic thromboembolism, congestive heart failure (CHF) and stroke.[5][6][8][12] The Framingham study noted that LAE may be a risk factor for ischemic stroke in men partially mediated by LV mass.[2] However, the role and basic characteristics of LAE in acute cerebral infarction patients have not been sufficiently described in the literature. Especially, the relation between stroke subtypes and LAE is not clear in patients with acute ischemic stroke. In this study, we investigated the relation of LAE at the time of acute ischemic stroke with conventional stroke risk factors and stroke subtypes.

MATERIALS AND METHODS

Subjects and clinical data

The enrolled study population included 182 patients with acute ischemic stroke (mean age: 68.01 ± 12.53 years and 106 males), who were admitted from September 2010 to June 2011 and examined with brain magnetic resonance imaging (MRI).

Clinical data were collected through medical record review or direct interview. Routine laboratory tests included complete blood counts, glucose, serum electrolytes, coagulation studies, liver function tests, and lipid profile. Systemic hypertension was defined as systolic blood pressure values > 140 mm Hg or diastolic blood pressure > 90 mm Hg during the interview, or the presence of a medical history or antihypertensive treatment. Diabetes mellitus was identified based on of elevated fasting blood glucose level, positive medical history, or current antidiabetic treatment. Hyperlipidemia was determined by a fasting total cholesterol level higher than 220 mg/dL, or antilipid agent treatment. Coronary artery disease included the presence of an abnormal diagnostic test (stress test or coronary angiography), a history of typical angina or myocardial infarction, or appropriate drug treatment. Atrial fibrillation was identified by a current or past electrocardiography or Holter monitoring. CHF was defined based on symptoms, clinical signs, and/or anti-failure treatment. Valvular heart disease was evaluated by 2-dimensional transthoracic echocardiography. Previous stroke was indicated by a positive history on the medical record.

Stroke subtypes

Stroke subtypes were sorted in to 5 classes based on the National Institute of Neurological Disorders and Stroke and Trial of Org 10171 in Acute Stroke Treatment (TOAST) criteria as follows:[1] 1) Large artery atherosclerosis included patients with clinical and brain imaging findings of either significant (> 50%) stenosis or occlusion of a major brain artery or cortical artery branch, probably due to atherosclerosis. 2) Cardioembolism was defined as patients with cerebral infarction probably due to an embolus originated in the heart. Possible large artery atherosclerotic sources of thrombosis or embolism should be excluded. 3) Small artery occlusion (lacuna) included patients with classical lacunar syndromes and no evidence of cardiac embolism and significant large artery stenosis. The patient should also have a significant posterior fossa level or hemispheric subcortical lesion with a diameter of less than 1.5 cm on neuroimaging. 4) Patients with rare causes of stroke such as non-atherosclerotic vasculopathies, hypercoagulable states, or hematologic disorders were classified as the category of other cause. 5) Patients whose cause of a stroke cannot be identified with any degree of evidence were labeled as unknown cause. Diagnostic evaluations included laboratory assessments, neuroimaging (MRI, etc.), electrocardiogram, cardiac imaging (echocardiography, etc.), and duplex ultrasound imaging of extracranial arteries.

Echocardiographic data

Transthoracic echocardiography was performed for all patients within 30 days of diagnosis of cerebral infarction. Studies and measurements were taken based on the guidelines of the American Society of

Echocardiography.[15] Measurement of left atrial anteroposterior diameter especially was performed according to a leading edge-to-leading edge convention at the aortic valve level. Indexed left atrial volume (LAVI) was calculated from the left atrial anteroposterior diameter indexed to body surface area. Echocardiographic LAE was identified when the LAVI was larger than 27 mL/m^2.

Statistical analyses

The data collected included continuous variables (clinical and echocardiographic data) and categorical variables (stroke risk factors). Continuous variables are presented as the mean ± standard deviation (SD). Differences in baseline characteristics between stroke patients with normal and increased LAVI were analyzed by using an unpaired, 2-tailed Student's *t*-test. Differences of stroke risk factors between patients with and without LAE in the categorical variable values were evaluated using the chi-square test. Null hypotheses of no difference were rejected if *p* values were less than 0.05, or, equivalently, if the 95% confidence intervals (CIs) of risk point estimates excluded 1. Logistic regression analysis was employed to determine the correlation of stroke subtypes and increased LAVI. All statistical analysis has been performed using SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Demographic characteristics of participants are presented in Table 1. The mean LAVI of all study subjects was 37.62 ± 17.59 ml/m^2. One hundred thirty eight (75.8 %) of patients had increased LAVI (42.58 ± 17.40 ml/m^2). Patients with normal LAVI were 44 (24.2 %) whose mean LAVI was 22.09 ± 3.39 ml/m^2. Age and sex were not significantly different between those with increased LAVI and normal LAVI. Patients with increased LAVI tend to have more stroke risk factors than patients with normal LAVI. Patients with increased LAVI were significantly different from patients with normal LAVI in the prevalence of hypertension (81.2% VS 52.3%; p = 0.000), history of previous stroke (21% VS 6.8%; p = 0.031), atrial fibrillation (29.7% VS 4.5%; p = 0.001), and valvular heart disease including mitral stenosis (17.4% VS 2.3%; p = 0.011) but not in the prevalence of coronary artery disease, CHF and diabetes mellitus.

Patients with increased LAVI commonly had cardioembolic stroke subtype (41, 29.7%) compared with patients with small vessel occlusion (38, 27.5%), large vessel atherosclerosis (36, 26.0%), and unknown (20,

Table 1. Demographic characteristics

		N = 182	LAE (N = 138)	Normal LA (N = 44)	*p* value
Age (mean)		68.01 ± 12.53	67.76 ± 12.90	68.80 ± 11.40	0.076
Sex	Male	106 (58.2%)	75 (54.3%)	31 (70.5%)	0.635
	Female	76 (41.8%)	63 (45.7%)	13 (29.5%)	
HTN		135 (74.2%)	112 (81.2%)	23 (52.3%)	0.000
DM		75 (41.2%)	56 (40.6%)	19 (43.2%)	0.760
CHF		24 (13.2%)	21 (15.2%)	3 (6.8%)	0.152
CAD		13 (7.1%)	10 (7.2%)	3 (6.8%)	0.923
Valvular heart disease		25 (13.7%)	24 (17.4%)	1 (2.3%)	0.011
Atrial fibrillation		45 (24.7%)	41 (29.7%)	2 (4.5%)	0.001
Hypercholesterolemia		62 (34.1%)	42 (30.4%)	20 (45.5%)	0.067
Previous stroke		32 (17.6%)	29 (21.0%)	3 (6.8%)	0.031

LAE= left atrial enlargement; LA= left atrium; HTN= hypertension; DM= diabetes mellitus; CHF= congestive heart failure; CAD= coronary artery disease.

Table 2. Stroke subtypes and LAE

Stroke subtypes	Mean LAVI (ml/m^2)	LAE n, (%)	Normal LA n, (%)
All subjects (n = 182)	37.62	138	44
SVD (n = 60, 33.0%)	29.72	38 (27.5%)	22 (50%)
LAD (n = 50, 27.5%)	34.61	36 (26.0%)	14 (31.8%)
CE (n = 45, 24.7%)	53.29	41 (29.7%)	4 (9%)
Undetermined (n = 24, 13.2%)	34.47	20 (14.4%)	4 (9%)
Other cause (n = 3, 1.6%)	36.16	3 (2.1%)	0

LAE= left atrial enlargement; LA= left atrium; LAVI= indexed left atrial volume; SVD= small vessel disease; LAD= large artery disease; CE= cardioembolism.

14.4%) subtype (Table 2). The proportion of LAE in patients with cardioembolic stroke subtype was significantly high, namely, 41 patients had increased LAVI while only 4 patients had normal LAVI.

An increased LAVI was associated with a cardioembolic subtype compared with small vessel disease (Table 3). An increased LAVI risk was present after adjustment for age and sex, and the adjusted odds ratio was 6.749 (p = 0.002) compared with small vessel disease.

DISCUSSION

The major findings of this study were as follows: first, increased LAVI is more common in patients who had cardiovascular risk factors, such as hypertension, valvular heart disease, atrial fibrillation, and previous stroke. Second, increased LAVI influences most patients in all ischemic stroke subtypes, and is especially highly prevalent in the cardioembolic stroke subtype. Therefore, increased LAVI is more likely a risk factor of ischemic stroke, especially cardioembolic stroke, than normal LAVI.

There are suggestions that LAE is associated with the risk of stroke.[5)6)9)11)] A recent study in a hypertensive population revealed that a first-ever ischemic stroke was associated with LAE, and LAVI was the best predictor of stroke in left atrial assessment.[11)] They enrolled a hypertensive population with or without first ischemic stroke as study population and there were no differences in ischemic heart disease, paroxysmal atrial fibrillation and heart failure between groups. They showed, however, that paroxysmal atrial fibrillation and other stroke risk factors are associated with LAE in stroke patients with hypertension. One study reported that for patients with first-ever ischemic stroke in an ethnically diverse population, LAE was associated with an elevated risk of cerebral infarction after adjustment for other stroke risk factors in acute ischemic stroke patients with significantly increased mean left atrial anteroposterior diameter and LAVI compared with control group.[5)] Another study found that 75% of first ischemic stroke patients have increased LAVI.[6)] Ischemic stroke patients with increased LAVI were older and had more cardiovascular risk factors than those with normal LAVI. LAVI was also associated with mortality after adjusted for multiple risk factors. The current study has similar results in that patients with increased LAVI have more cardiovascular risk factors and previous stroke history.

Left atrium (LA) volume is related to severity and chronicity of diastolic dysfunction in the absence of severe valvular disease and atrial fibrillation. The poor LV compliance raises LA pressure to retain ad-

Table 3. Statistical analyses of risk of ischemic stroke subtypes according to LAE

Stroke subtypes	p value	Odds ratio
LAD	0.346	1.500
CE	0.002	6.749
Undetermined	0.115	2.641

LAE= left atrial enlargement; LAD= large artery disease; CE= cardioembolism.

equate LV filling during ventricular diastole. Continuous exposure to abnormal LV filling pressure may result in LA remodeling and LAE. Few previous researchers have shown LAE associated with risk of CHF. The Cardiovascular Health Study observed an independent relation of LA volume in the patient group with a higher incidence and prevalence of CHF compared with control group.[8] In a study of elderly subjects with preserved LV systolic function, LAVI larger than 32 mL/m^2 was seen to independently predict first CHF.[14] Contrary to those results, this study found no significant difference in the prevalence of CHF between patients with and without LAE. This is possibly due to the age difference of the studied subjects. The subject population of this study was younger than previous studies, in which subjects ≥ 65 years of age were enrolled.

The mechanisms of the relation between ischemic stroke and an LAE are not completely understood. A potential explanation is that the increased hemostasis and thrombus formation might arise as the left atrial size increases. The thrombogenicity of an enlarged LA is suggested by the results of several transesophageal echocardiographic studies.[10][13] Research to determine possible intracardiac sources of cerebral emboli report that LAE is the best predictor for either clot in left atrial appendage or spontaneous echo contrast.[10] An enlarged atrial size may be the consequence of a raised intra-atrial pressure, which diminishes the flow velocity in the left atrial appendage and therefore increases the thrombogenicity and the embolic risk.[13] LAE has been reported to be a potent risk factor for the development of atrial fibrillation. The Framingham Heart Study showed that every 5 mm increment in LA size raised the risk of atrial fibrillation by 39%.[16] The Cardiovascular Health Study noted that LAE was an independent risk factor of new onset atrial fibrillation in older adults and LA with larger than 0.5 mm diameter had a 4-fold risk of new atrial fibrillation.[12] These observations may explain part of the association between stroke and LAE.

This study has a few limitations. There is potential for intrinsic selection bias in the sample because this study enrolled patients having echocardiography at the time of stroke. The study population has relatively small sample size to represent the general characteristics of ischemic stroke patients fully and there is no proper control group to strengthen the results. Further study remains to be performed on a large population and with a normal control group.

CONCLUSION

LAE is relatively common finding in patients with ischemic stroke. However, there was a lack of investigations about clinical characteristics and considerations as a stroke risk factor. From the results of this study, LAE was found to be a significant risk factor of ischemic stroke, particularly in case of cardioembolic stroke subtype. It may be useful in the estimation of stroke risk and treatment of ischemic stroke in the clinical field.

REFERENCES

1. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993 Jan;24(1):35-41.
2. Benjamin EJ, D'Agostino RB, Belanger AJ, Wolf PA, Levy D. Left atrial size and the risk of stroke and death. The Framingham Heart Study. Circulation. 1995 Aug;92(4):835-41.
3. Bihorac A, Tezcan H, Ozener C, Oktay A, Akoglu E. Association between salt sensitivity and target organ damage in essential hypertension. Am J Hypertens. 2000 Aug;13(8):864-72.
4. Bonita R, Beaglehole R. Does treatment of hypertension explain the decline in mortality from stroke? Br Med J (Clin Res Ed). 1986 Jan;292(6514):191-2.
5. Di Tullio MR, Sacco RL, Sciacca RR, Homma S. Left atrial size and the risk of ischemic stroke in an ethnically mixed population. Stroke. 1999 Oct;30(10):2019-24.
6. Fatema K, Bailey KR, Petty GW, Meissner I, Osranek M, Alsaileek AA et al. Increased left atrial volume index: Potent biomarker for first-ever ischemic stroke. Mayo Clin Proc. 2008 Oct;83(10):1107-15.
7. Gorelick PB. Stroke prevention. An opportunity for effi-

cient utilization of health care resources during the coming decade. Stroke. 1994 Jan;25(1):220-4.

8. Gottdiener JS, Kitzman DW, Aurigemma GP, Arnold AM, Manolio TA. Left atrial volume, geometry, and function in systolic and diastolic heart failure of persons > or = 65 years of age (the cardiovascular health study). Am J Cardiol. 2006 Jan;97(1):83-9.
9. Lai CL, Chien KL, Hsu HC, Su TC, Chen MF, Lee YT. Left atrial dimension and risk of stroke in women without atrial fibrillation: The Chin-Shan community cardiovascular cohort study. Echocardiography. 2011 Nov;28 (10):1054-60.
10. Lee RJ, Bartzokis T, Yeoh TK, Grogin HR, Choi D, Schnittger I. Enhanced detection of intracardiac sources of cerebral emboli by transesophageal echocardiography. Stroke. 1991 Jun;22(6):734-9.
11. Piotrowski G, Banach M, Gerdts E, Mikhailidis DP, Hannam S, Gawor R et al. Left atrial size in hypertension and stroke. J Hypertens. 2011 Oct;29(10):1988-93.
12. Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP et al. Incidence of and risk factors for atrial fibrillation in older adults. Circulation. 1997 Oct;96(7):2455-61.
13. Tabata T, Oki T, Fukuda N, Iuchi A, Manabe K, Kageji Y et al. Influence of left atrial pressure on left atrial appendage flow velocity patterns in patients in sinus rhythm. J Am Soc Echocardiogr. 1996 Nov-Dec;9(6):857-64.
14. Takemoto Y, Barnes ME, Seward JB, Lester SJ, Appleton CA, Gersh BJ et al. Usefulness of left atrial volume in predicting first congestive heart failure in patients > or = 65 years of age with well-preserved left ventricular systolic function. Am J Cardiol. 2005 Sep;96(6):832-6.
15. Tsang T, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. Am J Cardiol. 2002 Dec;90 (12):1284-9.
16. Vaziri SM, Larson MG, Benjamin EJ, Levy D. Echocardiographic predictors of nonrheumatic atrial fibrillation. The Framingham Heart Study. Circulation. 1994 Feb;89(2):724-30.
17. Suh OJ, Rheu SO. The Cause of death Statistics. Department of Population Trend. Statistics Korea. 2012.