Higher Left Ventricle Mass Indices Predict Favorable Outcome in Stroke Patients with Thrombolysis

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Background: We sought to assess the association of left ventricle mass (LVM) indices with the functional outcome of acute ischemic stroke (AIS) patients after intravenous tissue plasminogen activator (IV-tPA). *Methods:* Consecutive AIS patients with IV-tPA were recruited. LVM indices including LVM/weight, LVM/surface, and LVM/height$^{2.7}$ on echocardiogram during hospitalization were retrospectively reviewed. Outcome was 90-day modified Rankin scale (mRS) scores. Multivariate logistic regression was performed to analyze the association of LVM indices with outcome. *Results:* Between August 2010 and May 2014, 55 AIS patients (age range from 27 to 78 years, 69.1% men) with echocardiogram after thrombolysis were recruited. Lower baseline National Institutes of Health Stroke Scale (NIHSS; $P = .009$) and higher LVM indices (LVM/weight [$P = .012$], LVM/surface [$P = .039$], and LVM/height$^{2.7}$ [$P = .045$]) were significantly associated with 90-day favorable outcome (mRS, 0-2). In multivariate logistic regression analysis, LVM/weight independently predicted good outcome with an odds ratio of 3.89 (95% confidence interval, 1.05-14.42, $P = .042$) after adjustment for baseline NIHSS, onset-to-treatment time, hypertension, hemorrhagic transformation, and systolic left ventricle inner diameters. *Conclusions:* Higher LVM indices on echocardiogram are significantly associated with favorable outcome in stroke patients with IV-tPA, among which LVM/weight seems to be the most effective. **Key Words:** Echocardiogram—thrombolysis—left ventricle mass—stroke outcome.

Ischemic stroke is one of the leading causes of death and the first cause of disability in industrialized countries.[1] Systemic thrombolysis with intravenous tissue plasminogen activator (IV-tPA) is the only Food and Drug Administration–approved reperfusion therapy within 4.5 hours from symptom onset.[2] Recently, researches are trying to reveal the association between cardiac function and ischemic stroke.[3,4]

Left ventricular hypertrophy (LVH) is considered to be a consequence of chronically increased left ventricular afterload. Echocardiographically estimated left ventricle mass (LVM) indices including LVM/surface, LVM/height, and LVM/height$^{2.7}$ are effective for the detection of LVH, which could provide important prognostic information.[5,6] Obesity causes intrinsic changes in the heart including an increase in LVM.[7] Several researches in rats have explored the significance of LVM/weight.[8] However, the predictive role of LVM indices in acute ischemic stroke (AIS) patients with IV-tPA has not been established yet.

We sought to assess the association of LVM indices with the functional outcome of AIS patients after IV-tPA. We hypothesized LVM indices, especially LVM/weight,

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might be of useful utilities to predict the outcome in AIS patients.

Methods

Patients

We identified AIS patients presenting to our institution between August 2010 and May 2014 within 4.5 hours of stroke symptom onset who received IV-tPA from our prospectively recorded stroke database. Those with routine echocardiogram during admission were recruited. Baseline National Institutes of Health Stroke Scale (NIHSS), onset-to-treatment time (OTT), height, weight, and risk factors were obtained from the database. The study was performed with the informed consent of subjects or next of kin and with ethical approval from the institutional review boards of Huashan Hospital.

Echocardiogram

Echocardiograms were performed in the left lateral decubitus position using standard imaging planes according to the American Society of Echocardiography recommendations[9] during hospitalization after IV-tPA. Left ventricular end-diastolic diameter, ventricular septal thickness, and posterior wall thickness in end-diastole were measured in end-diastole. The LVM was calculated using the following formula[10]: LVM (g) = .806 × (1.046 × [{ventricular septal thickness + left ventricular end-diastolic diameter + posterior wall thickness}^{3} − {left ventricular end-diastolic diameter}^{3}]) + .6 g. LVM indices were presented with LVM/weight (LVM divided by weight), LVM/height (LVM divided by height), LVM/height$^{2.7}$ (LVM divided by height$^{2.7}$), and LVM/surface (LVM divided by body surface area).

Computed Tomography (CT)/Magnetic Resonance Imaging (MRI)

CT scans of the brain were taken and assessed before IV-tPA and 24 hours after IV-tPA. Other CT scans were taken if necessary. Several patients undertook MRI 24 hours after thrombolysis. Hemorrhagic transformation (HT) was defined according to the European Cooperative Acute Stroke Study on CT as an area of increased attenuation within an area of low attenuation in a typical vascular distribution.[11] On MRI, HT was identified by the presence of blood-product signal characteristics on T1, T2, and gradient-echo sequences.[12]

Outcome Measures

The primary outcome was disability at day 90 (3-month visit), as assessed by means of the modified Rankin scale (mRS) scores, dichotomized as favorable outcome (score of 0-2) or unfavorable outcome (score of 3-6). The secondary outcome was early neurologic improvement (ENI) defined with NIHSS score 24 hours post-treatment improvement by 40% from baseline.

Statistical Analysis

Statistical analyses were performed using SPSS, version 21 (SPSS Inc., Chicago, IL). P value less than .05 was considered to indicate statistical significance. Differences in patients' characteristics between outcomes were tested by chi-square or Fisher exact test for categorical and Mann–Whiney for continuous values. Spearman's nonparametric rank correlation was performed to assess the correlation between different LVM indices. Multivariate logistic regression (including variables with $P < .10$ and $P < .15$) was used to assess the association of variables with favorable outcome. Receiver operating characteristic analysis was performed to determine the optimal threshold of LVM/weight in predicting 90-day mRS (0-2).

Results

From August 2010 to May 2014, one hundred sixty-eight patients within 4.5 hours of stroke symptom onset received IV-tPA in our institution. Of those, 55 patients had echocardiograms after admission. There was no significant difference in baseline characteristics and 90-day functional outcome in these patients compared with the entire population. And 67.3% (37 of 55) of patients achieved favorable functional outcome with 90-day mRS 0-2. Hemorrhagic transformation occurred in 9.1% (5 of 55) of the patients and was associated with poor functional outcome ($P = .035$). Three patients died at 90-day follow-up.

As for the different LVM indices, LVM/weight showed good correlation with LVM/surface (r = .95, $P < .01$) and LVM/height$^{2.7}$(r = .84, $P < .01$).

Patient's characteristics in total and stratified by outcomes are listed in Table 1 and Table 2. Lower baseline NIHSS ($P = .009$), higher LVM/weight ($P = .012$), higher LVM/surface ($P = .039$), and higher LVM/height$^{2.7}$ ($P = .045$) were significantly associated with good functional outcome (90-day mRS 0-2).

In multivariate logistic regression analysis of factors with P value less than .1, LVM/weight, LVM/surface, and LVM/height$^{2.7}$ were able to predict 90-day functional outcome with odds ratio (OR) 5.02 (95% confidence interval [CI], 1.39-15.16), 1.04 (95% CI, 1.00-1.07), and 1.06 (95% CI, 1.00-1.13), respectively, after adjustment for baseline NIHSS and hemorrhagic transformation. Moreover, in multivariate logistic regression analysis of factors with P value less than .15, the association remained significant between LVM/weight and outcome (OR, 3.89; 95% CI, 1.05-14.42; $P = .042$) after adjustment for baseline NIHSS, OTT, hypertension, hemorrhagic transformation, and systolic left ventricle inner diameters (Table 3).

Table 1. *Baseline clinical characteristics of patients stratified by outcome and in total*

Variables	Total	mRS 0-2	mRS 3-6	*P* value
N	55	37	18	
Age (y)	65 (59, 72)	63 (57, 72)	67 (61, 72)	.369
Male	69.1% (38/55)	70.3% (26/37)	66.7% (12/18)	.786
Weight (kg)	68 (60, 75)	68 (60,75)	69 (59,80)	.387
Hypertension	63.6% (35/55)	70.3% (26/37)	50.0% (9/18)	.143
Diabetes	32.7% (18/55)	35.1% (13/37)	27.8% (5/18)	.585
Dyslipidemia	23.6% (13/55)	24.3% (9/37)	22.2 (4/18)	1.000
Smoking	50.9% (28/55)	54.1% (20/37)	44.4% (8/18)	.504
Atrial fibrillation	36.4% (20/55)	32.4% (12/37)	44.4% (8/18)	.385
Previous stroke	20.0% (11/55)	18.9% (7/37)	22.2% (4/18)	1.000
IHD	16.4% (9/55)	13.5% (5/37)	22.2% (4/18)	.454
Baseline NIHSS	9 (5, 14)	8 (4, 12)	14 (6, 16)	.009
OTT (min)	170 (130, 215)	180 (138, 229)	154 (114,190)	.125
HT	9.1% (5/55)	2.7% (1/37)	22.2% (4/18)	.035
Etiology of stroke				.813
Large-artery disease	34.5% (19/55)	32.4% (12/37)	38.9% (7/18)	
Cardioembolism	23.6% (13/55)	27.0% (10/37)	16.7% (3/18)	
Small-vessel disease	34.5% (19/55)	32.4% (12/37)	38.9% (7/18)	
Others	7.3% (4/55)	8.1% (3/37)	5.6% (1/18)	

Abbreviations: HT, hemorrhagic transformation; IHD, ischemia heart diseases; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; OTT, onset-to-treatment time.

In receiver operating characteristic analysis, increased LVM/weight, LVM/surface, and LVM/height$^{2.7}$ were associated with 90-day mRS (0-2) with area under curve of .71 (95% CI, .56-.86; P = .012), .67 (95% CI, .51-.84; P = .039), and .67 (95% CI, .51-.83; P = .045), respectively (Figure 1). The optimal threshold of LVM/weight determined by Youden's index was 2.28 for functional outcome. The threshold of LVM/weight greater than 2.28 predicted good functional outcome (mRS 0-2) with sensitivity of 84% (31 of 37), specificity of 56% (10 of 18), and positive predictive value of 80% (31 of 39).

Nineteen patients were diagnosed with large-vessel occlusions, and 42.1% (8 of 19) achieved ENI. Higher LVM/weight (P = .007) and higher LVM/surface (P = .026) were significantly associated with ENI.

Discussion

This study showed higher LVM indices on echocardiogram were significantly associated with favorable outcome in stroke patients with IV-tPA. LVM/weight was the most effective marker to predict outcome. Higher LVM/weight was associated with favorable outcome independent of baseline NIHSS, OTT, hypertension, hemorrhagic transformation, and systolic left ventricle inner diameters. These results suggest LVM/weight, especially greater than 2.28, may be clinically useful as a marker of good prognosis after ischemic stroke with IV-tPA.

LVH plays a central role in chronic adaptation to pressure or volume overload of the systemic circulation. The degree of hypertrophy parallels the severity of the

Table 2. *Echocardiogram measurements of patients stratified by outcome and in total*

Variables	Total	mRS 0-2	mRS 3-6	*P* value
N	55	37	18	
LVIDs	31 (28, 33)	32 (29, 33)	30 (25,34)	.115
LVEF	65 (61, 69)	65 (62,69)	64 (60,69)	.815
LVM	175.6 (137.1, 219.8)	181.9 (150.3, 222.8)	149.9 (109.8, 211.8)	.062
LVM/surface	101.5 (75.8, 120.3)	101.8 (90.4, 125.9)	75.6 (67.7, 111.7)	.039
LVM/height$^{2.7}$	44.3 (36.4, 53.6)	44.8 (38.8, 54.4)	36.7 (29.1, 50.8)	.045
LVM/height	104.6 (81.6, 129.8)	113.7 (88.9, 132.3)	88.1 (69.3, 124.8)	.067
LVM/weight	2.51 (2.05, 3.26)	2.68 (2.34, 3.42)	2.15 (1.77, 2.85)	.012

Abbreviations: LVIDs, systolic left ventricle inner diameters; LVEF, left ventricle ejection fraction; LVM, left ventricle mass; mRS, modified Rankin scale.

Table 3. *Multivariate logistic regression for 90-day good outcome (mRS 0-2)*

Predictors	OR	95% CI	*P* value
Baseline NIHSS*	.85	.74-.98	.022
HT	3.28	.25-42.37	.363
LVM/surface	1.04	1.00-1.07	.029
Baseline NIHSS*	.86	.75-.98	.024
HT	3.35	.26-43.00	.353
LVM/height$^{2.7}$	1.06	1.00-1.13	.048
Baseline NIHSS*	.85	.73-.98	.022
HT	3.59	.27-47.22	.332
LVM/weight	5.02	1.39-15.16	.014
Baseline NIHSS†	.84	.72-.97	.02
OTT(min)	1.01	.99-1.02	.343
Hypertension	1.76	.40-7.70	.450
HT	2.93	.17-51.04	.462
LVIDs	1.06	.88-1.28	.532
LVM/weight	3.89	1.05-14.42	.042

Abbreviations: CI, confidence interval; HT, hemorrhagic transformation; LVIDs, systolic left ventricle inner diameters; LVM, left ventricle mass; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; OTT, onset-to-treatment time.

*Logistic regression in factors with $P < .1$.

†Logistic regression in factors with $P < .15$.

overload, and detection of extreme hypertrophy may indicate a poor prognosis.[13] LVM is defined with various variables or algorithms, including body surface area, height, and height$^{2.7}$ for different diagnostic criteria of LVH.[6,14,15] LVM/weight is currently used in researches of rats as an index of cardiac hypertrophy.[8] Only 1 study

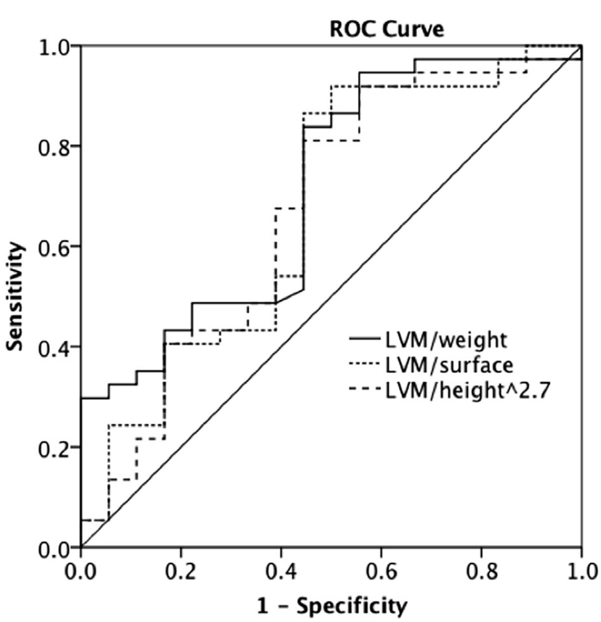

Figure 1. *ROC curve of LVM indices in predicting the good functional outcome. Abbreviations: ROC, receiver operating characteristic; LVM, left ventricle mass.*

has assessed the predictive role of cardiac function in AIS patients with IV-tPA and revealed that clinical diagnosis of heart failure only predicts 90-day mortality but not disability.[16] Palumbo et al[16] adopted left ventricle ejection fraction (LVEF) less than 40%, which predicted mortality, but not disability, in acute stroke patients undergoing thrombolysis. However, there was no patient with LVEF less than 40% in our study (the minimum LVEF was 44%), and we did not find any significant differences in LVEF between the functional outcomes. We tested the value of LVM/weight in stroke patients with IV-tPA and successfully proved LVM/weight was the most powerful outcome predictor among LVM indices. The threshold of LVM/weight greater than 2.28 achieved a good sensitivity and a moderate specificity.

LVH has been proved to increase the risk of stroke and transient ischemic attack.[17] However, in our study, among a certain population consisting of AIS patients with IV-tPA, increased LVM indices acted as protective factors. Similar to the phenomenon that smoking is a proven risk factor of stroke but can increase the effect of IV-tPA after acute stroke,[18] the particular mechanism explaining the relationship between LVH and increased risk of stroke but heightened effect of IV-tPA is unclear.

For AIS patients with large-vessel occlusion, recanalization could be assessed by follow-up CT angiography, MR angiography, or transcranial Doppler ultrasound. Kharitonova et al[19] proposed that ENI defined with NIHSS improvement by 40% could be used as a surrogate marker for recanalization after intravenous thrombolysis in AIS when angiographic examinations were not available. In our study, patients with higher LVM indices were more likely to achieve ENI possibly associated with a higher recanalization rate.

However, some other possibilities might be considered. First, increased myocardial oxygen consumption with LVH might lead to chronic cerebral ischemia,[20] and the development of improved small-vessel cerebral collaterals and subsequent better cerebral perfusion.[21] Second, it has been previously reported that in the compensatory phase of the LVH, vascular endothelial growth factor (VEGF) is significantly unregulated.[22] VEGF mediates collateral growth in ischemic disease[23,24] and contributes to more robust collateral grade, which associates with better clinical outcomes.[25,26] Meanwhile, VEGF can enhance angiogenesis in the ischemic brain and improve neurologic recovery.[27] These or other changes of brain metabolism in LVH might limit the initial impairment and influence stroke progression. These avenues warrant further investigation.

Limitations of our study were due to the small sample size and derived from a single-center experience. Stroke subtype–based analysis between long-term functional outcome and LVM indices was not available considering a limited sample size. Meanwhile, because fulfillment of echocardiograms was an inclusion criterion, patients with unconsciousness or symptomatic hemorrhage who could not cooperate to receive echocardiogram were not included. Only 32.7% (55 of 168) with adequate echocardiogram measures recruited might possibly reduce the power of the result. At last, because cardiac adaption was chronic, longer time of follow-up might be reasonable. Further study needs to validate our findings in a prospective cohort.

References

1. Donnan GA, Fisher M, Macleod M, et al. Stroke. Lancet 2008;371:1612-1623.
2. Jauch EC, Saver JL, Adams HP, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44:870-947.
3. Gongora-Rivera F, Labreuche J, Jaramillo A, et al. Autopsy prevalence of coronary atherosclerosis in patients with fatal stroke. Stroke 2007;38:1203-1210.
4. Sharma JC, Ross I, Vassallo M. Cardioprotection in acute stroke. Int J Stroke 2007;2:288-290.
5. Bikkina M, Levy D, Evans JC, et al. Left ventricular mass and risk of stroke in an elderly cohort. JAMA 1994; 272:33-36.
6. Levy D, Garrison RJ, Savage DD, et al. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham heart study. N Engl J Med 1990;322:1561-1566.
7. Lakhani M, Fein S. Effects of obesity and subsequent weight reduction on left ventricular function. Cardiol Rev 2011;19:1-4.
8. Li ZC, Yu HY, Wang XX, et al. Olmesartan medoxomil reverses left ventricle hypertrophy and reduces inflammatory cytokine IL-6 in the renovascular hypertensive rats. Eur Rev Med Pharmacol Sci 2013;17:3318-3322.
9. Sahn DJ, DeMaria A, Kisslo J, et al. Recommendations regarding quantitation in M-mode echocardiography. Circulation 1978;58:1072-1083.
10. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986;57: 450-458.
11. Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: the European Cooperative Acute Stroke Study (ECASS). JAMA 1995;274:1017-1025.
12. Jain AR, Jain M, Kanthala AR, et al. Association of CT perfusion parameters with hemorrhagic transformation in acute ischemic stroke. AJNR 2013;34:1895-1900.
13. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. Circulation 1977;55:613-618.
14. Levy D, Anderson KM, Savage DD, et al. Echocardiographically detected left ventricular hypertrophy: prevalence and risk factors. Ann Intern Med 1988;108:7-13.
15. de Simone G, Daniels SR, Devereux RB, et al. Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. J Am Coll Cardiol 1992;20: 1251-1260.
16. Palumbo V, Baldasseroni S, Nencini P, et al. The coexistence of heart failure predicts short-term mortality, but not disability, in patients with acute ischemic stroke treated with thrombolysis: the Florence area Registry. Eur J Intern Med 2012;23:552-557.
17. Bouzas-Mosquera A, Broullón FJ, Álvarez-García N, et al. Association of left ventricular mass with all-cause mortality, myocardial infarction and stroke. PLoS One 2012; 7:e45570.
18. Kufner A, Nolte CH, Galinovic I, et al. Smoking-thrombolysis paradox: recanalization and reperfusion rates after intravenous tissue plasminogen activator in smokers with ischemic stroke. Stroke 2013;44:407-413.
19. Kharitonova T, Mikulik R, Roine RO, et al. Association of early National Institutes of Health Stroke Scale improvement with vessel recanalization and functional outcome after intravenous thrombolysis in ischemic stroke. Stroke 2011;42:1638-1643.
20. Houghton JL, Frank MJ, Carr AA, et al. Relations among impaired coronary flow reserve, left ventricular hypertrophy and thallium perfusion defects in hypertensive patients without obstructive coronary artery disease. J Am Coll Cardiol 1990;15:43-51.
21. Liebeskind DS. Collateral circulation. Stroke 2003;34: 2279-2284.
22. Huusko J, Lottonen L, Merentie M, et al. AAV9-mediated VEGF-B gene transfer improves systolic function in progressive left ventricular hypertrophy. Mol Ther 2012; 20:2212-2221.
23. Biscetti F, Pecorini G, Straface G, et al. Cilostazol promotes angiogenesis after peripheral ischemia through a VEGF-dependent mechanism. Int J Cardiol 2013;167: 910-916.
24. Lucitti JL, Mackey JK, Morrison JC, et al. Formation of the collateral circulation is regulated by vascular endothelial growth factor-A and a disintegrin and metalloprotease family members 10 and 17. Circ Res 2012;111: 1539-1550.
25. Liebeskind DS, Tomsick TA, Foster LD, et al. Collaterals at angiography and outcomes in the Interventional Management of Stroke (IMS) III trial. Stroke 2014;45:759-764.
26. Marks MP, Lansberg MG, Mlynash M, et al. Effect of collateral blood flow on patients undergoing endovascular therapy for acute ischemic stroke. Stroke 2014; 45:1035-1039.
27. Zhang ZG, Zhang L, Jiang Q, et al. VEGF enhances angiogenesis and promotes blood-brain barrier leakage in the ischemic brain. J Clin Invest 2000;106:829-838.