JACC: CARDIOVASCULAR IMAGING VOL. 11, NO. 3, 2018

PUBLISHED BY ELSEVIER

ORIGINAL RESEARCH

Left Ventricular Geometry Determines Prognosis and Reverse J-Shaped Relation Between Blood Pressure and Mortality in Ischemic Stroke Patients

Chan Soon Park, MD,[a] Jun-Bean Park, MD, PhD,[a] Yerim Kim, MD,[b] Yeonyee E. Yoon, MD,[a,c] Seung-Pyo Lee, MD, PhD,[a] Hyung-Kwan Kim, MD, PhD,[a] Yong-Jin Kim, MD, PhD,[a] Goo-Yeong Cho, MD, PhD,[a,c] Dae-Won Sohn, MD, PhD,[a] Seung-Hoon Lee, MD, PhD[d]

ABSTRACT

OBJECTIVES This study sought to investigate the prognostic significance of left ventricular (LV) mass and geometry in ischemic stroke survivors, as well as the LV geometry-specific differences in the blood pressure-mortality relationship.

BACKGROUND LV mass and geometry are well-known prognostic factors in various populations; however, there are no data on their role in ischemic stroke patients.

METHODS We prospectively recruited 2,328 consecutive patients admitted with acute ischemic stroke to our institute between 2002 and 2010. Of these, 2,069 patients were analyzed in whom echocardiographic data were available to assess LV mass and geometry.

RESULTS All-cause mortality was significantly greater in patients with concentric hypertrophy (adjusted hazard ratio [HR]: 1.417; 95% confidence interval [CI]: 1.045 to 1.920) and concentric remodeling (HR: 1.540; 95% CI: 1.115 to 2.127) but nonsignificantly in those with eccentric hypertrophy (HR: 1.388; 95% CI: 0.996 to 1.935) compared with normal geometry in multivariate analyses. Relative wall thickness was a significant predictor of all-cause mortality (HR: 1.149 per 0.1-U increase in relative wall thickness; 95% CI: 1.021 to 1.307), whereas LV mass index was not (HR: 1.003 per 1 g/m^2 increase in LV mass index; 95% CI: 0.999 to 1.007). Similar results were observed with cardiovascular mortality. In multivariable fractional polynomials, patients with altered LV geometry showed reverse J-curve relationships between acute-phase systolic blood pressure and all-cause or cardiovascular mortality, with the highest risks in the lower extremes, whereas those with normal geometry did not.

CONCLUSIONS Echocardiographic assessment of LV geometry provided independent and additive prognostic information in ischemic stroke patients. A reverse J-shaped relation of mortality with blood pressure was found in patients with abnormal LV geometry. (J Am Coll Cardiol Img 2018;11:373-82) © 2018 by the American College of Cardiology Foundation.

Stroke is a highly prevalent disease and the second-leading cause of mortality in the world (1). Ischemic stroke is the most common type of stroke and has a substantial case fatality rate (1,2). For this reason, various attempts have been made to enhance clinical outcomes after ischemic stroke, including the identification of potential prognosticators such as the National Institutes of Health Stroke

From the [a]Cardiovascular Center, Seoul National University Hospital, Seoul, Republic of Korea; [b]Kangdong Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Republic of Korea; [c]Cardiovascular Center, Seoul National University Bundang Hospital, Seongnam, Gyeonggi-do, Republic of Korea; and the [d]Department of Neurology, Seoul National University College of Medicine, Seoul, Republic of Korea. This study was supported by 2 grants from the government of Korea: Basic Science Research Program through the National Research Foundation (NRF-2015R1A2A2A01007770), funded by the Ministry of Science, ICT and Future Planning, and Korean Health Technology Research and Development Project (HI13C1961), funded by the Ministry for Health, Welfare and Family Affairs. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Jun-Bean Park and Seung-Hoon Lee contributed equally to this work.

Manuscript received October 21, 2016; revised manuscript received January 30, 2017, accepted February 7, 2017.

ISSN 1936-878X/$36.00 http://dx.doi.org/10.1016/j.jcmg.2017.02.015

ABBREVIATIONS AND ACRONYMS

AUC = area under the curve

BP = blood pressure

CBF = cerebral blood flow

LV = left ventricular

LVMi = left ventricular mass index

NIHSS = National Institutes of Health Stroke Scale

RWT = relative wall thickness

Scale (NIHSS) (3). Indeed, recent studies showed a temporal trend of a decrease in both stroke incidence and mortality along with improvements in the control of risk factors, in particular hypertension (4). However, the mortality rates were still unacceptably high after incident ischemic strokes (533 of 929; 57.4%) (4), which suggests the need for better risk stratification and tailored treatment to further improve clinical outcomes.

In the diagnostic work-up of ischemic stroke patients, transthoracic echocardiography is widely performed to determine the presence of cardioembolic sources (5). Given that echocardiography provides useful prognostic information in various diseases (6,7), it can also be used as a practical tool to stratify patients with ischemic stroke according to risk. Specifically, one study demonstrated that the risk of developing stroke was associated with left ventricular (LV) mass and geometry measured by echocardiography (8). In spite of these previous reports, there are no data on the prognostic value of LV geometry for the prediction of long-term outcomes in patients after acute ischemic stroke, except for lacunar stroke (9).

SEE PAGE 383

Among risk factors for ischemic stroke, high blood pressure (BP) is a major contributor, not only to its development but also to poor outcomes after acute ischemic stroke (10,11). Conversely, there have been concerns about whether ischemic stroke patients with BP below certain cutoff values, even within normal range, are associated with grave prognosis (12). In particular, among patients with underperfused but still viable brain tissue (i.e., penumbra), any fall in BP can increase the infarct area by reducing the survival of penumbra, subsequently resulting in stroke progression. In this regard, pressure-dependent cerebral blood flow (CBF) for penumbra has been suggested as a plausible mechanism for a U- or J-shaped curve, with higher mortality rates at low BP and at very high BP in ischemic stroke patients (13,14). Furthermore, the threshold of low BP that leads to a reduced cerebral perfusion can be different depending on the severity and duration of the underlying hypertension (15,16). Given that adverse cardiac remodeling reflects myocardial response to pressure overload integrated over time, including hypertension (17), it can be speculated that patients with different LV geometric patterns could have different BP cutoff values for impaired cerebral perfusion and potentially poor clinical outcomes after ischemic stroke than those with concentric forms of remodeling.

In this study, we investigated the prognostic value of LV mass and geometry in predicting mortality after acute ischemic stroke. We also hypothesized that the adverse influence of low BP on mortality would be more prominent in stroke patients with altered LV geometry than in those with a normal geometry.

METHODS

STUDY DESIGN AND PARTICIPANTS. The design of the registry has been described elsewhere (18). Briefly, this prospective registry was designed to include consecutive patients with acute ischemic stroke (i.e., <7 days from stroke onset). Only patients with available echocardiographic recordings were eligible for this study. Exclusion criteria were diagnoses of intracerebral hemorrhage, subarachnoid hemorrhage, or in-hospital stroke. Among 2,328 patients recruited from October 2002 to September 2010, the final sample size was 2,069 for this study, because individuals were further excluded for the following reasons: poor echocardiographic image (n = 174), insufficient anthropometric data (n = 47), significant valvular heart disease (n = 36), and hypertrophic cardiomyopathy (n = 2). The institutional review board of the Seoul National University Hospital approved the study protocol (H-1009-062-332), and written informed consent was obtained from all participants or from the next of kin when it was not possible to obtain the patient's agreement.

DATA COLLECTION. We recorded baseline demographic, clinical, and laboratory data for all patients. We defined acute post-stroke BP as the first BP measured in the emergency department or other area (19).

Ischemic stroke subtype was assessed by stroke physicians on the basis of clinical and radiological data and classified into 5 categories according to TOAST (Trial of Org 10172 in Acute Stroke Treatment) (20): 1) large-artery atherosclerosis; 2) small-artery occlusion; 3) cardioembolism; 4) stroke of other origin; and 5) stroke of undetermined origin. In addition to 5 original subtypes, transient ischemic attack was included in the analysis, which was defined as an episode of focal neurological deficit that resolved within 24 h and was attributed to focal cerebral ischemia. The initial neurological severity was estimated with the NIHSS score at admission (21). Body surface area was calculated by the DuBois and DuBois formula. Brain magnetic resonance imaging was obtained with a 1.5-T or 3.0-T system and was performed according to a standard protocol (22). Significant carotid artery stenosis was defined as luminal diameter narrowing ≥50% in

the internal carotid artery. Body mass index was calculated as measured body weight divided by height squared (kg/m^2) and categorized as obese and nonobese groups according to previous studies with modification for Asian populations (23–25).

MORTALITY DATA. Patients were closely followed up at the stroke clinic of our institute at 3-month intervals. All-cause and cardiovascular deaths were used as outcome variables. Mortality data, including the date of death and cause of death, were collected from the governmental statistics office in South Korea (19). Cardiovascular death was defined as death of stroke, myocardial infarction, cardiac arrhythmia, heart failure, pulmonary embolism, or other cardiovascular causes.

ECHOCARDIOGRAPHIC ANALYSIS. Echocardiography was performed according to the recommendations of the American Society of Echocardiography (26,27) using commercially available systems. Among various methods used to assess LV geometry and architecture, such as sphericity index (28,29), we classified LV geometry according to the report of Verma et al. (6). Echocardiographic variables included left ventricular end-diastolic internal diameter (LVIDd), LV end-systolic internal diameter, interventricular septum thickness at end diastole (IVSTd), and posterior wall thickness at end diastole (PWTd). LV mass was calculated on the basis of standard methods currently recommended (27,30): LV mass = 0.80 × (1.04 × [(IVSTd + LVIDd + PWTd)^3 − LVIDd^3]) + 0.6. LV mass was then indexed to body surface area, and LV hypertrophy was defined as echocardiography-derived left ventricular mass index (LVMi) >115 g/m^2 for men and >95 g/m^2 for women (6,27,30). Regional wall thickness (RWT) was calculated as: 2 × (PWTd)/(LVIDd), and increased RWT was defined when this ratio was >0.42 for both men and women (6,27,30). Patients were classified into 4 groups of LV geometric pattern based on LVMi and RWT: normal geometry (normal LVMi and normal RWT), eccentric hypertrophy (LV hypertrophy and normal RWT), concentric remodeling (normal LVMi and increased RWT), and concentric hypertrophy (LV hypertrophy and increased RWT).

STATISTICAL ANALYSIS. Data were presented as numbers and frequencies for categorical variables and as mean ± SD for continuous variables. For comparison between groups, the chi-square test or Fisher exact test was used for categorical variables and the unpaired Student *t* test for continuous variables, as appropriate. One-way analysis of variance and Scheffé post hoc test were used to analyze differences for continuous variables among more than 2 groups. The chronological trend of outcomes was expressed as Kaplan-Meier estimates and compared according to LV geometry. The log-rank test was performed for comparison of the differences in clinical outcomes. We calculated the area under the curve (AUC) by receiver operating characteristic analysis, net reclassification improvement, and integrated discrimination improvement to evaluate the predictive value of LV geometry for mortality. A multivariable Cox proportional hazards regression model was used to find the independent predictors of all-cause and cardiovascular death. Variables associated with mortality with a p value <0.05 in univariate analysis were included as confounding variables in multivariate analysis. To assess potential differences in relationships between mortality and BP in different LV geometric patterns, patients were stratified into those with normal or abnormal LV geometry, and then the associations between systolic BP and all-cause or cardiovascular death were modeled with Cox regression, and nonlinearities were explored with multivariable fractional polynomials (31). Two-sided p values <0.05 were considered significant. Statistical tests were performed with STATA software version 12 (Stata Corp., College Station, Texas).

RESULTS

BASELINE CHARACTERISTICS. Among all study patients, the prevalence of overweight and obesity was 27.9% and 35.9%, respectively. Baseline characteristics according to LV geometry are summarized in **Table 1**. Briefly, patients with normal geometry were younger; more frequently male; less likely to have a history of diabetes mellitus, hypertension, or hyperlipidemia; and likely to have lower body mass index. Stroke severity, measured by NIHSS score, was greatest in patients with eccentric hypertrophy, followed by those with concentric hypertrophy, concentric remodeling, and normal geometry. There were no significant differences in the use of medications or interventional or surgical treatments among groups.

RELATION OF LV GEOMETRY TO MORTALITY AFTER ISCHEMIC STROKE. During a median follow-up of 37.6 months, 367 patients (18%) died of all causes and 166 (8%) of cardiovascular causes. Patients who died had more adverse baseline characteristics, such as older age, higher prevalence of hypertension and diabetes mellitus, previous history of atrial fibrillation, or higher NIHSS score than those who survived (Online Table 1).

When classified according to LV geometric patterns, unadjusted all-cause mortality was higher in patients with abnormal geometry than in those with normal geometry (concentric remodeling, log-rank p = 0.006;

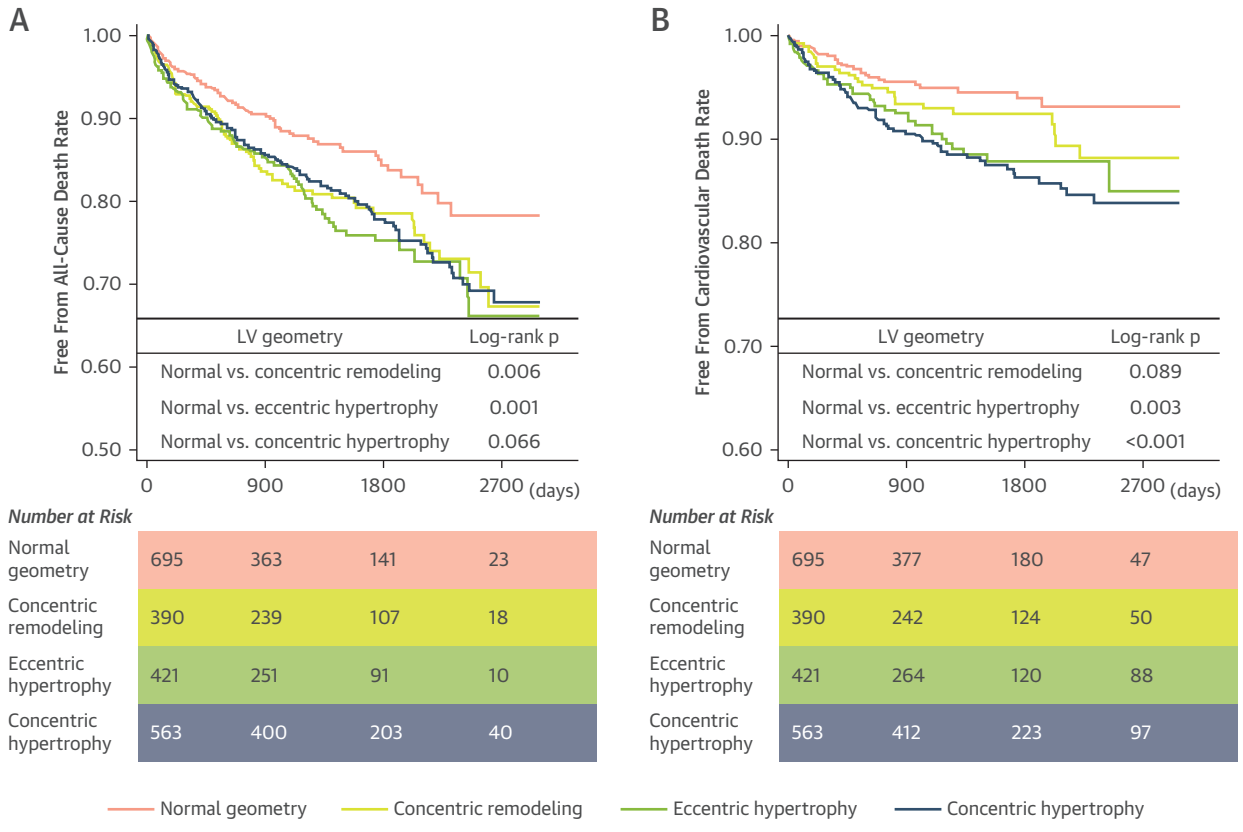
TABLE 1 Baseline Characteristics Stratified by LV Geometric Patterns (N = 2,069)

	Normal Geometry (n = 695)	Concentric Remodeling (n = 390)	Eccentric Hypertrophy (n = 421)	Concentric Hypertrophy (n = 563)	p Value
Demographic data					
Age, yrs	62.5 ± 13.9	65.4 ± 11.7	67.5 ± 10.9	66.7 ± 11.1	<0.001
Men	73.2	77.7	38.2	54.9	<0.001
Blood pressure, mm Hg					
Systolic	146.0 ± 24.7	150.9 ± 26.5	152.0 ± 27.3	159.0 ± 28.5	<0.001
Diastolic	84.3 ± 14.6	86.4 ± 15.4	85.2 ± 15.8	89.4 ± 17.9	<0.001
Body mass index					
Value, kg/m^2	23.7 ± 3.1	23.9 ± 3.1	24.0 ± 3.4	24.7 ± 3.4	<0.001
Classification					0.002
Nonobese	68.6	65.1	63.4	58.3	
Obese	31.4	34.9	36.6	41.7	
Past medical history					
Diabetes mellitus	27.3	37.9	30.9	36.4	<0.001
Hypertension	51.7	66.2	68.2	79.9	<0.001
Hyperlipidemia	20.6	22.6	23.5	26.6	0.088
Smoking	41.4	42.6	24.2	32.1	<0.001
Transient ischemic attack	5.1	5.9	3.1	4.1	0.220
Stroke	18.4	20.9	17.7	22.3	0.212
TOAST stroke classification (% of overall patients)					<0.001
Large-artery atherosclerosis (28.6%)	30.8	31.8	24.1	27.2	
Small-vessel occlusion (25.7%)	21.6	28.4	27.0	28.0	
Cardioembolism (17.1%)	16.3	13.2	20.8	17.9	
Stroke of other determined origin (3.0%)	4.5	3.1	2.6	1.3	
Stroke of undetermined origin (19.5%)	19.1	16.8	21.2	20.4	
Transient ischemic attack (6.1%)	7.7	6.7	4.3	5.2	
Laboratory findings					
Leukocytes, per μl	7,867.3 ± 2,773.9	7,987.7 ± 2,962.7	7,571.0 ± 2,653.4	7,993.1 ± 2,775.0	0.085
Hemoglobin, mg/dl	13.9 ± 1.9	14.0 ± 1.8	13.1 ± 1.9	13.7 ± 1.8	<0.001
Total cholesterol, mg/dl	175.8 ± 37.5	182.3 ± 39.3	178.2 ± 39.0	183.0 ± 39.4	0.004
HDL, mg/dl	44.6 ± 12.9	44.2 ± 12.2	45.2 ± 12.7	44.0 ± 12.7	0.550
Triglycerides, mg/dl	119.5 ± 64.2	134.1 ± 75.6	124.4 ± 76.5	140.1 ± 83.4	<0.001
LDL, mg/dl	107.5 ± 32.8	111.6 ± 34.0	108.0 ± 34.1	111.1 ± 33.7	0.113
FBS, mg/dl	107.3 ± 34.6	115.8 ± 40.4	110.2 ± 36.6	115.9 ± 47.0	<0.001
HbA_{1c}, %	6.3 ± 1.2	6.6 ± 1.4	6.4 ± 1.2	6.5 ± 1.4	<0.001
Electrocardiography and echocardiography findings					
Atrial fibrillation	12.5	13.3	17.3	16.5	0.071
Ejection fraction, %	61.9 ± 7.0	63.3 ± 6.6	58.1 ± 10.5	62.1 ± 7.8	<0.001
Magnetic resonance angiography					
Carotid artery stenosis ≥50%	9.4	13.5	10.0	9.5	0.160
Neurological severity					
NIHSS score	4.1 ± 4.8	4.6 ± 5.2	4.9 ± 5.4	4.8 ± 5.2	0.029
Medication at discharge					
Antiplatelet medication	78.3	78.2	75.5	76.0	0.622
Anticoagulation management	22.9	22.6	26.8	25.0	0.384
Intervention during admission					
Thrombolysis	7.1	6.7	9.0	7.5	0.570
Craniectomy	0.6	0.3	0.7	1.4	0.186
Endarterectomy	0.0	0.0	0.0	0.2	0.444
Angioplasty	2.7	3.8	3.1	2.7	0.715

Values are mean ± SD or %.

BP = blood pressure; FBS = fasting blood sugar; HbA_{1c} = glycated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LV = left ventricular; NIHSS = National Institutes of Health Stroke Scale; TOAST = Trial of Org 10172 in Acute Stroke Treatment.

FIGURE 1 **Impact of LV Geometry on Mortality in Ischemic Stroke Patients**



Kaplan-Meier curves showed a difference in freedom from all-cause **(A)** and cardiovascular **(B)** death after ischemic stroke based on LV geometry. LV = left ventricular.

eccentric hypertrophy, log-rank p = 0.001; and concentric hypertrophy, log-rank p = 0.066) (Figure 1A). The risk of cardiovascular mortality was also higher in patients with concentric remodeling (log-rank p = 0.089), eccentric hypertrophy (log-rank p = 0.003), and concentric hypertrophy (log-rank p < 0.001) than in those with normal geometry (Figure 1B).

Table 2 shows the results from the Cox proportional hazard models. Univariate analyses demonstrated that all abnormal LV geometric patterns were significantly associated with an increased risk of all-cause death. In multivariate analyses, concentric remodeling and concentric hypertrophy were significant determinants for all-cause death, whereas eccentric hypertrophy showed nonsignificance. Similar findings were observed with cardiovascular death. Subgroup analysis in patients with carotid artery stenosis <50% showed that concentric remodeling or concentric hypertrophy was associated with worse outcomes in this subpopulation (Online Table 2). When analyzed as continuous variables, LVMi and RWT were significant univariate determinants of all-cause or cardiovascular death. Multivariate analyses also showed that the LVMi and RWT remained independent predictors of all-cause or cardiovascular death, whereas the association between LVMi and all-cause death was nonsignificant.

INCREMENTAL PROGNOSTIC VALUE OF LV GEOMETRY OVER NIHSS SCORE. The addition of LV geometry to NIHSS score significantly increased the AUC for predicting cardiovascular death (from 0.703 to 0.734; p = 0.024) but not for all-cause death (from 0.672 to 0.684; p = 0.176) (Table 3). When LVMi and RWT were incorporated with NIHSS score as continuous variables, it significantly increased the AUC for all-cause death (from 0.672 to 0.699; p = 0.009) and for cardiovascular death (from 0.703 to 0.751; p = 0.001). The addition of either LV geometry or LVMi and RWT also improved the measures of reclassification (i.e., net reclassification improvement and integrated discrimination improvement) for all-cause or cardiovascular death.

TABLE 2 Unadjusted and Adjusted Cox Regression Analysis for All-Cause and Cardiovascular Mortality

	Univariate Analysis			Multivariate Analysis*		
	HR	95% CI	p Value	HR	95% CI	p Value
All-cause death						
Categorical variables						
Normal geometry (reference)	1.000					
Concentric remodeling	1.537	1.127–2.097	0.007	1.540	1.115–2.127	0.009
Eccentric hypertrophy	1.652	1.219–2.240	0.001	1.388	0.996–1.935	0.053
Concentric hypertrophy	1.491	1.124–1.976	0.006	1.417	1.045–1.920	0.025
Continuous variables						
LVMi	1.008	1.005–1.011	<0.001	1.003	0.999–1.007	0.096
RWT × 10	1.144	1.029–1.272	0.013	1.149	1.021–1.307	0.022
Cardiovascular death						
Categorical variables						
Normal geometry (reference)	1.000					
Concentric remodeling	1.557	0.938–2.584	0.087	1.723	1.024–2.898	0.040
Eccentric hypertrophy	2.007	1.252–3.217	0.004	1.589	0.955–2.644	0.075
Concentric hypertrophy	2.254	1.471–3.454	<0.001	1.851	1.167–2.937	0.009
Continuous variables						
LVMi	1.013	1.009–1.018	<0.001	1.006	1.001–1.012	0.025
RWT × 10	1.301	1.123–1.507	<0.001	1.258	1.053–1.504	0.012

*HRs have been adjusted by age, sex, systolic blood pressure, obesity, smoking history, previous history of stroke, TOAST classification, ejection fraction, leukocyte, hemoglobin, HbA_{1c}, carotid artery stenosis, and NIHSS score when admitted.

CI = confidence interval; HR = hazard ratio; LVMi = left ventricular mass index; RWT = relative wall thickness; other abbreviations as in Table 1.

REVERSE J-SHAPED ASSOCIATION BETWEEN SYSTOLIC BP AND MORTALITY. The Cox model with multivariable fractional polynomials showed that the risk of all-cause death decreased as systolic BP decreased in patients with normal LV geometry (Figure 2A); however, in patients with abnormal LV geometry, all-cause death risk increased at both extremes of systolic BP, with a steeper increase in the lower extreme (Figure 2B). With regard to cardiovascular death, this reverse J-shaped association was also found in patients with abnormal LV geometry (Figure 2D) but not in those with normal geometry (Figure 2C). Accordingly, mortality risks were lowest for a systolic BP of ≈150 to 160 mm Hg in ischemic stroke patients with abnormal LV geometry, in contrast to those with normal geometry, in whom a BP lower than this value conferred lower mortality. There was a significant interaction between the LV geometry groups and BP for all-cause and cardiovascular mortality (p for interaction = 0.041 and 0.044, respectively).

DISCUSSION

The major findings of this study are as follows: 1) the LV geometric pattern was an independent

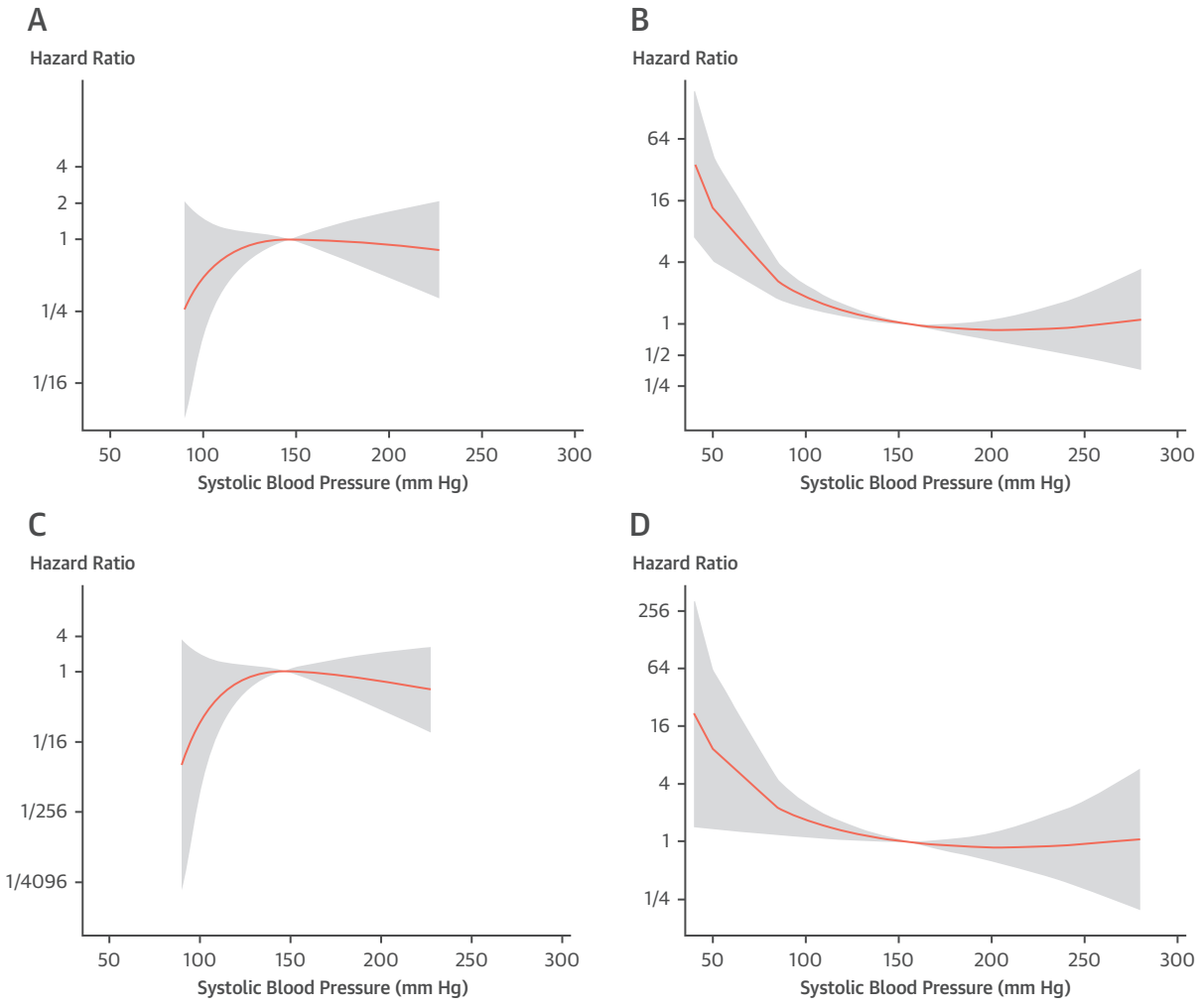
TABLE 3 Impact of Adding LV Geometry to NIHSS Score on Predicting Outcomes

	AUC		Category-Free NRI		IDI	
	Value	p Value	Value	p Value	Value	p Value
All-cause death						
NIHSS score (reference)*	0.672	–	–	–	–	–
NIHSS score + LV geometry	0.684	0.176	0.213	<0.001	0.008	<0.001
NIHSS score + LVMi + RWT	0.699	0.009	0.231	<0.001	0.016	<0.001
Cardiovascular death						
NIHSS score (reference)*	0.703	–	–	–	–	–
NIHSS score + LV geometry	0.734	0.024	0.354	<0.001	0.012	0.002
NIHSS score + LVMi + RWT	0.751	0.001	0.305	0.081	0.020	0.003

*Results of NIHSS score were taken as reference values for analyses.

AUC = area under the curve; IDI = integrated discrimination improvement; NRI = net reclassification improvement; other abbreviations as in Tables 1 and 2.

FIGURE 2 **Association Between Acute Post-Stroke Blood Pressure and Adjusted Mortality**



Adjusted fractional polynomial Cox regression showed the relationship between acute post-stroke systolic blood pressure and all-cause **(A and B)** or cardiovascular **(C and D)** mortality, according to left ventricular geometry (normal geometry, **A and C**; abnormal geometry, **B and D**). **Orange line** indicates hazard ratio, **shaded area** indicates 95% confidence interval. Hazard ratios were adjusted by age, systolic blood pressure, ejection fraction, leukocyte, hemoglobin, glycated hemoglobin, and National Institutes of Health Stroke Scale score at admission.

determinant of all-cause or cardiovascular death in ischemic stroke patients; 2) the addition of LV geometry to NIHSS score significantly improved the predictive ability for all-cause or cardiovascular death in this population; and 3) a lower systolic BP portended a higher mortality rate in stroke patients with abnormal LV geometry but not in those with normal geometry. An increased hemodynamic load, either pressure, volume, or a combination of both, contributes to the increase in LV mass and/or chamber dilation, resulting in different LV geometric adaptations, such as concentric remodeling, eccentric hypertrophy, and concentric hypertrophy (32). Hence, it is not surprising that the role of LV mass or geometry in relation to clinical outcomes has been well investigated and established in patients with hypertension, which is one of the most important causes of pressure overload on the LV (7,17,33). Furthermore, LV mass and geometry have been considered a cumulative indicator that reflects the severity and chronicity of cardiovascular risk factors, which suggests their potential to be better prognosticators than the traditional ones. In this regard, the clinical significance of LV mass and geometry has been extensively explored in various cardiovascular diseases, including coronary artery

disease (34), post-myocardial infarction (6), and preserved LV ejection fraction (23). However, there is a paucity of data on the prognostic implications of LV geometry in patients with ischemic stroke, although it has been reported that LV hypertrophy and abnormal geometry are associated with an increased risk of developing ischemic stroke (8).

Our data demonstrated that concentric hypertrophy and concentric remodeling conveyed higher mortality after ischemic stroke than normal LV geometry, which was in line with previous studies; however, the insignificant association between eccentric hypertrophy and adverse outcomes is distinct from other studies. This difference can be explained in part by the previous findings that cardiovascular resistance and cerebral perfusion were different according to LV geometric pattern (17). Specifically, among those with abnormal LV geometric patterns, patients with eccentric hypertrophy had the lowest cardiovascular resistance and highest cardiac index, which led to improved cerebral perfusion. Given that the maintenance of cerebral perfusion is a critical determinant of the extent of ischemic brain injury (35), it can be speculated that lower cardiovascular resistance in patients with eccentric hypertrophy might contribute to fewer adverse consequences after ischemic stroke.

Mortality rates for ischemic stroke remain high despite recent progress in risk factor control and treatment, which highlights the need to develop a better risk stratification and tailored treatment strategy. Our study showed that the assessment of LV mass or geometry provided an incremental prognostic value above that of the NIHSS score to predict all-cause or cardiovascular death in patients with acute ischemic stroke. Given that echocardiography is one of the most commonly performed tests to evaluate for a cardioembolic source of stroke, echocardiography-based assessment of LV geometry can be a practical and useful clinical tool to improve risk prediction and management in ischemic stroke patients.

A J-curve association between BP and worse prognosis of cardiovascular events has been reported repeatedly (36,37). Clinicians are often faced with difficulties in deciding whether to lower raised BP after acute ischemic stroke, because previous studies reported that although 84% of stroke patients had elevated BP on admission (38), BP usually decreased spontaneously, and only one-third of the patients remained hypertensive (39). Our study showed that BP on the first and fourth days after admission was lower than that on admission (Online Figure 1), which suggests initial post-stroke BP might be influenced by various factors such as pain or anxiety. Furthermore, the concern with lowering BP in ischemic stroke patients is additional loss of viable brain tissue because of worse hypoperfusion than the penumbral threshold.

In physiological conditions, the detrimental effects of low BP on brain tissue can be prevented by cerebral autoregulation, a homeostatic mechanism to maintain CBF nearly constant when cerebral perfusion pressure or systemic BP changes (40). However, previous studies suggested that patients with long-standing hypertension have a right-shifted autoregulation curve (15,16). Thus, low BP values in patients with chronic hypertension can cause cerebral hypoperfusion and further ischemic insult, whereas similar BP values are within the range of cerebral autoregulation in patients without underlying hypertension. Indeed, a previous study suggested that the clinical outcome of lowering BP in ischemic stroke patients might be related to accustomed long-term BP (19). On the other hand, given that altered LV geometry can be a time-integrated indicator of chronic pressure overload, it can be hypothesized that patients with abnormal LV geometry have an increased probability of right-shifted autoregulation curves compared with those with normal geometry.

In the present study, intriguingly, only patients with abnormal LV geometry demonstrated an elevated mortality risk associated with a lower acute post-stroke BP, contrary to their counterparts. These findings on the LV geometry-specific association between BP and mortality support the hypothesis that hypertension contributes to both adverse LV remodeling and impaired autoregulation of cerebral, coronary, or renal blood flow (Online Figure 2) (41-43) and suggest a potential role for assessment of LV geometric patterns in guiding decisions regarding the optimal BP target in ischemic stroke patients. Further studies are required to validate these hypothetical explanations. Another possibility is that patients with abnormal LV geometry were more aggressively treated to lower BP than those with normal geometry, which means that overly aggressive BP lowering, rather than LV geometry, could be a major cause of poor outcomes. However, when we evaluated BP changes according to mortality, there was no significant difference in the magnitude of BP reduction during hospital stay between patients who survived and those who died within the follow-up period. On the other hand, patients with abnormal LV geometry had significantly higher values of systolic BP but similar magnitudes of systolic BP reduction during the first 5 days compared with those with normal geometry (Online Figures 3A and 3B). These findings could support our speculation about

possible right-shifted CBF autoregulation curves in patients with abnormal LV geometry.

STUDY LIMITATIONS. First, we used the cutoff values of LVMi and RWT published in previous studies, which did not include people of East Asian ethnicity as subjects. A recent study showed that the upper reference values of LVMi were lower for East Asian than European men, whereas those of RWT were similar between the 2 groups (44), which suggests that cutoff values of LVMi for hypertrophy could also be different for East Asians. However, there was no evidence for the ethnicity-specific cutoffs to define LV hypertrophy or increased RWT. Furthermore, similar results were found when we analyzed LVMi and RWT as continuous variables. Second, we excluded patients who did not have echocardiographic measurements at admission, which could have introduced inclusion bias favoring less ill patients who were able to undergo echocardiography. Third, we could not clearly explain the relatively high prevalence of concentric remodeling and concentric hypertrophy in this study. This finding might be explained in part by the evidence that concentric forms of remodeling can be prevalent in stroke patients who were enrolled relatively recently (9). Finally, although a different subtype of stroke, particularly cardioembolic stroke, can have an entirely different pathophysiology, we could not evaluate our findings according to stroke subtype.

CONCLUSIONS

In patients with acute ischemic stroke, LV geometry is an independent and incremental prognostic factor for all-cause and cardiovascular mortality. Only patients with abnormal LV geometry have a reverse J-shaped relationship between acute post-stoke BP and all-cause or cardiovascular mortality, with higher mortality risks for lower systolic BP values.

ADDRESS FOR CORRESPONDENCE: Dr. Jun-Bean Park, Cardiovascular Center, Seoul National University Hospital, Room 9623, 101 Daehak-ro, Jongno-gu, Seoul 110-744, Republic of Korea. E-mail: nanumy1@gmail.com OR Dr. Seung-Hoon Lee, Department of Neurology, Seoul National University Hospital, Room 11604, 101 Daehak-ro, Jongno-gu, Seoul 110-744, Republic of Korea. E-mail: sb0516@snu.ac.kr.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: There are few data on the prognostic value of LV geometry in patients with ischemic stroke, even though LV geometry reflects the chronicity and severity of cardiovascular risks. Currently available data also do not provide an optimal target BP during the acute phase of ischemic stroke.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Echocardiography is a widely used imaging technique for the evaluation of patients with acute ischemic stroke. Echocardiography-based assessment of LV geometry can provide prognostic information in ischemic stroke patients and help identify the subgroup of individuals with increased mortality risks at low BP levels.

TRANSLATIONAL OUTLOOK: Further studies are required to elucidate whether therapeutic strategies to achieve different target levels of acute post-stroke BP guided by LV geometry can improve prognosis in ischemic stroke patients.

REFERENCES

1. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol 2009;8:355–69.

2. Hartmann A, Rundek T, Mast H, et al. Mortality and causes of death after first ischemic stroke: the Northern Manhattan Stroke Study. Neurology 2001;57:2000–5.

3. Adams HP Jr., Davis PH, Leira EC, et al. Baseline NIH stroke scale score strongly predicts outcome after stroke: a report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). Neurology 1999;53:126–31.

4. Koton S, Schneider AL, Rosamond WD, et al. Stroke incidence and mortality trends in US communities, 1987 to 2011. JAMA 2014;312:259–68.

5. Rem JA, Hachinski VC, Boughner DR, Barnett HJ. Value of cardiac monitoring and echocardiography in TIA and stroke patients. Stroke 1985;16:950–6.

6. Verma A, Meris A, Skali H, et al. Prognostic implications of left ventricular mass and geometry following myocardial infarction: the VALIANT (VALsartan In Acute myocardial iNfarcTion) Echocardiographic Study. J Am Coll Cardiol Img 2008;1:582–91.

7. Verdecchia P, Schillaci G, Borgioni C, et al. Adverse prognostic significance of concentric remodeling of the left ventricle in hypertensive patients with normal left ventricular mass. J Am Coll Cardiol 1995;25:871–8.

8. Di Tullio MR, Zwas DR, Sacco RL, Sciacca RR, Homma S. Left ventricular mass and geometry and the risk of ischemic stroke. Stroke 2003;34:2380–4.

9. Field TS, Pearce LA, Asinger RW, et al., on behalf of the SPS3 Investigators. Left ventricular geometry on transthoracic echocardiogram and prognosis after lacunar stroke: the SPS3 trial. J Stroke Cerebrovasc Dis 2015;24:1423–9.

10. Willmot M, Leonardi-Bee J, Bath PM. High blood pressure in acute stroke and subsequent outcome: a systematic review. Hypertension 2004;43:18–24.

11. Ishitsuka K, Kamouchi M, Hata J, et al., for the FSR Investigators. High blood pressure after acute ischemic stroke is associated with poor clinical outcomes: Fukuoka Stroke Registry. Hypertension 2014;63:54–60.

12. Fischer U, Rothwell PM. Blood pressure management in acute stroke: does the Scandinavian Candesartan Acute Stroke Trial (SCAST) resolve all of the unanswered questions? Stroke 2011;42:2995–8.

13. Castillo J, Leira R, Garcia MM, Serena J, Blanco M, Davalos A. Blood pressure decrease during the acute phase of ischemic stroke is associated with brain injury and poor stroke outcome. Stroke 2004;35:520–6.

14. Lin MP, Ovbiagele B, Markovic D, Towfighi A. Systolic blood pressure and mortality after stroke: too low, no go? Stroke 2015;46:1307–13.

15. Zhang R, Witkowski S, Fu Q, Claassen JA, Levine BD. Cerebral hemodynamics after short- and long-term reduction in blood pressure in mild and moderate hypertension. Hypertension 2007; 49:1149–55.

16. Immink RV, van den Born BJ, van Montfrans GA, Koopmans RP, Karemaker JM, van Lieshout JJ. Impaired cerebral autoregulation in patients with malignant hypertension. Circulation 2004;110:2241–5.

17. Ganau A, Devereux RB, Roman MJ, et al. Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension. J Am Coll Cardiol 1992;19:1550–8.

18. Ryu WS, Lee SH, Kim CK, Kim BJ, Yoon BW. Increased serum alkaline phosphatase as a predictor of long-term mortality after stroke. Neurology 2010;75:1995–2002.

19. Fischer U, Cooney MT, Bull LM, et al. Acute post-stroke blood pressure relative to premorbid levels in intracerebral haemorrhage versus major ischaemic stroke: a population-based study. Lancet Neurol 2014;13:374–84.

20. Adams HP Jr., Bendixen BH, Kappelle LJ, et al., and the TOAST Investigators. Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial. Stroke 1993;24: 35–41.

21. Goldstein LB, Bertels C, Davis JN. Interrater reliability of the NIH stroke scale. Arch Neurol 1989;46:660–2.

22. Kwon HM, Kim BJ, Lee SH, Choi SH, Oh BH, Yoon BW. Metabolic syndrome as an independent risk factor of silent brain infarction in healthy people. Stroke 2006;37:466–70.

23. Lavie CJ, Milani RV, Ventura HO, Cardenas GA, Mehra MR, Messerli FH. Disparate effects of left ventricular geometry and obesity on mortality in patients with preserved left ventricular ejection fraction. Am J Cardiol 2007;100:1460–4.

24. Patel DA, Lavie CJ, Artham SM, Milani RV, Cardenas GA, Ventura HO. Effects of left ventricular geometry and obesity on mortality in women with normal ejection fraction. Am J Cardiol 2014; 113:877–80.

25. Hashimoto Y, Tanaka M, Okada H, et al. Metabolically healthy obesity and risk of incident CKD. Clin J Am Soc Nephrol 2015;10:578–83.

26. Choi JO, Shin MS, Kim MJ, et al. Normal echocardiographic measurements in a Korean population study: part I: cardiac chamber and great artery evaluation. J Cardiovasc Ultrasound 2015;23:158–72.

27. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1–39.e14.

28. Santos-Gallego CG, Vahl TP, Goliasch G, et al. Sphingosine-1-phosphate receptor agonist fingolimod increases myocardial salvage and decreases adverse postinfarction left ventricular remodeling in a porcine model of ischemia/reperfusion. Circulation 2016;133:954–66.

29. Mannaerts HF, van der Heide JA, Kamp O, Stoel MG, Twisk J, Visser CA. Early identification of left ventricular remodelling after myocardial infarction, assessed by transthoracic 3D echocardiography. Eur Heart J 2004;25:680–7.

30. Marwick TH, Gillebert TC, Aurigemma G, et al. Recommendations on the use of echocardiography in adult hypertension: a report from the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE). J Am Soc Echocardiogr 2015;28:727–54.

31. Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model continuous risk variables in epidemiology. Int J Epidemiol 1999; 28:964–74.

32. Lavie CJ, Patel DA, Milani RV, Ventura HO, Shah S, Gilliland Y. Impact of echocardiographic left ventricular geometry on clinical prognosis. Prog Cardiovasc Dis 2014;57:3–9.

33. Muiesan ML, Salvetti M, Monteduro C, et al. Left ventricular concentric geometry during treatment adversely affects cardiovascular prognosis in hypertensive patients. Hypertension 2004;43:731–8.

34. Ghali JK, Liao Y, Cooper RS. Influence of left ventricular geometric patterns on prognosis in patients with or without coronary artery disease. J Am Coll Cardiol 1998;31:1635–40.

35. Jauch EC, Saver JL, Adams HP Jr., 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.

36. Dorresteijn JA, van der Graaf Y, Spiering W, et al. Relation between blood pressure and vascular events and mortality in patients with manifest vascular disease: J-curve revisited. Hypertension 2012;59:14–21.

37. Yi SW, Mok Y, Ohrr H, et al. Low systolic blood pressure and vascular mortality among more than 1 million Korean adults. Circulation 2016;133: 2381–90.

38. Oppenheimer S, Hachinski V. Complications of acute stroke. Lancet 1992;339:721–4.

39. Britton M, Carlsson A, de Faire U. Blood pressure course in patients with acute stroke and matched controls. Stroke 1986;17:861–4.

40. Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation. Cerebrovasc Brain Metab Rev 1990;2:161–92.

41. Ruland S, Aiyagari V. Cerebral autoregulation and blood pressure lowering. Hypertension 2007; 49:977–8.

42. Polese A, De Cesare N, Montorsi P, et al. Upward shift of the lower range of coronary flow autoregulation in hypertensive patients with hypertrophy of the left ventricle. Circulation 1991; 83:845–53.

43. Almeida JB, Saragoca MA, Tavares A, Cezareti ML, Draibe SA, Ramos OL. Severe hypertension induces disturbances of renal autoregulation. Hypertension 1992;19 Suppl:II279–83.

44. Poppe KK, Doughty RN, Gardin JM, et al., for the Echocardiographic Normal Ranges Meta-Analysis of the Left Heart Collaboration. Ethnic-specific normative reference values for echocardiographic LA and LV size, LV mass, and systolic function: the EchoNoRMAL Study. J Am Coll Cardiol Img 2015;8:656–65.

KEY WORDS acute ischemic stroke, blood pressure, left ventricular geometry, left ventricular mass, mortality

APPENDIX For supplemental tables and figures, please see the online version of this paper.