

Association Between Left Ventricular Ejection Fraction, Wall Motion Abnormality, and Embolic Stroke of Undetermined Source

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Background—It is uncertain whether there is an association between left ventricular (LV) ejection fraction (LVEF) or LV wall motion abnormality and embolic stroke of undetermined source (ESUS).

Methods and Results—We performed a retrospective, cross-sectional study of patients with acute ischemic stroke enrolled in the CAESAR (Cornell Acute Stroke Academic Registry) from 2011 to 2016. We restricted this study to patients with ESUS and, as controls, those with small- and large-artery ischemic strokes. LVEF had to be above 35% to be considered ESUS. In a secondary analysis, we excluded patients with ESUS who had any evidence of ipsilateral carotid atherosclerosis. Multiple logistic regression was used to evaluate whether LVEF or LV wall motion abnormality was associated with ESUS. We performed a confirmatory study at another tertiary-care center. We identified 885 patients with ESUS (n=503) or small- or large-artery strokes (n=382). Among the entire cohort, LVEF was not associated with ESUS (odds ratio per 5% decrement in LVEF, 1.0; 95% CI, 1.0–1.1) and LV wall motion abnormality was not associated with ESUS (odds ratio, 0.9; 95% CI, 0.5–1.6). The results were identical in our confirmatory study. In our secondary analysis excluding ESUS patients with any evidence of ipsilateral carotid atherosclerosis, there was an association between LVEF and ESUS (odds ratio per 5% decrement in LVEF, 1.2; 95% CI, 1.0–1.5; $P=0.04$).

Conclusions—Among the entire cohort, no association existed between LVEF or LV wall motion abnormality and ESUS; however, after excluding ESUS patients with any evidence of ipsilateral carotid atherosclerosis, lower LVEF appeared to be associated with ESUS. (*J Am Heart Assoc.* 2019;8:e011593. DOI: 10.1161/JAHA.118.011593.)

Key Words: cardiac disease • echocardiography • ejection fraction • ischemic stroke

Cryptogenic stroke affects more than 200 000 patients in the United States each year. Most of these cryptogenic strokes appear embolic on imaging and are thus also referred to as embolic strokes of undetermined source (ESUS).^{1,2} It is suspected that a sizeable proportion of ESUS cases originate from the heart.³ Current guidelines classify ischemic strokes as cardioembolic when the left ventricular (LV) ejection

fraction (LVEF) is <30% to 35%.^{3,4} However, among patients without severely (<35%) reduced LV dysfunction, it is uncertain whether there exists an association between LVEF and stroke. Furthermore, it is unclear whether LV wall motion abnormality is independently associated with embolic stroke.⁵ Whereas LV akinesia or hypokinesia were previously considered risk factors for cardioembolism, recent evidence suggests that LV wall motion abnormality may not be associated with embolic stroke.^{5–7} In order to evaluate whether non-severely reduced LVEF or the presence of LV wall motion abnormality are associated with embolic stroke risk, we compared LVEF and LV wall motion abnormality between patients with ESUS and those with small- or large-artery ischemic strokes, who served as controls. We hypothesized that patients with ESUS would be more likely to have reduced LVEF and more likely to have LV wall motion abnormality as compared with patients with small- or large-artery strokes.

Methods

Design and Population

We performed a retrospective, cross-sectional study using data from the CAESAR (Cornell Acute Stroke Academic

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An abstract of this article was presented at the International Stroke Conference, February 6 to 8, 2019, in Honolulu, HI.

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Received November 27, 2018; accepted April 11, 2019.

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Clinical Perspective

What Is New?

- There does not appear to be an association between left ventricular ejection fraction or left ventricular motion abnormality and all patients with embolic stroke of undetermined source (ESUS).
- However, after excluding ESUS patients with any evidence of ipsilateral carotid atherosclerosis, lower left ventricular ejection fraction appeared to be associated with ESUS.

What Are the Clinical Implications?

- The results of our study suggest that nonseverely (<35%) reduced left ventricular ejection fraction may be a risk factor for a subset of patients with ESUS.
- In addition, the results of our study support the idea that ESUS likely represents a heterogeneous group of patients and add further credence to redefining the definition of ESUS into those with a likely cardioembolic mechanism of stroke which may respond to anticoagulation and those with a likely noncardioembolic mechanism of stroke, such as mild-to-moderate atherosclerotic disease, which may be less likely to respond to anticoagulation.

Registry). All patients hospitalized at NewYork–Presbyterian Hospital/Weill Cornell Medical Center for acute ischemic stroke are prospectively enrolled in the American Heart Association’s Get With The Guidelines (GWTG)–Stroke registry. Trained hospital analysts prospectively collect data on demographics, vascular risk factors and comorbidities, stroke severity, and in-hospital treatments and outcomes. CAESAR combines the GWTG data plus additional retrospectively collected clinical, laboratory, and radiographic data. The data that support the findings of this study are available from the corresponding author upon reasonable request. Patients’ underlying stroke mechanism was independently adjudicated by a panel of 3 neurologists who adjudicate the cause of stroke per the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification and per the recently proposed definitions for ESUS.^{3,4} In accord with the TOAST classification for cardioembolism, the LVEF had to be above 35% to be considered ESUS. In addition, given the conflicting data regarding whether LV wall motion abnormality is associated with increased stroke risk, we did not consider isolated LV wall motion abnormality to be a cardioembolic stroke mechanism.^{6,7} For this analysis, we included all adult patients with acute ischemic stroke registered in CAESAR from January 1, 2011 through December 31, 2016. Furthermore, we excluded patients who had strokes adjudicated as cardioembolic or “other” known mechanisms besides small- or large-artery strokes, such as dissection or vasculitis. Additionally,

we excluded patients who did not have a complete stroke workup, which consisted of brain magnetic resonance imaging or computed tomography, head and neck vessel imaging, at least 24 hours of cardiac telemetry, and echocardiography within 14 days of index stroke. Patients identified as having atrial fibrillation before or during the index stroke hospitalization were considered to have a cardioembolic stroke and were excluded from this analysis. Our final cohort included 885 patients with acute ischemic stroke, among whom 503 (57%) had ESUS and 382 (43%) had small- or large-artery strokes (Figure). Weill Cornell’s institutional review board approved this study with a waiver for the right to informed consent.

Measurements

In our primary analysis, we evaluated the association between LVEF and ESUS. LVEF estimation was based on transthoracic or transesophageal echocardiography results performed within 14 days of index stroke. An attending cardiologist formally interpreted all echocardiograms. In patients who had more than 1 echocardiogram performed, we included the LVEF of the echocardiogram performed closest to the index stroke. In addition, we evaluated the association between LV wall motion abnormality and ESUS. Presence of LV wall motion abnormality was similarly based on transthoracic or -esophageal echocardiography results, as interpreted by an

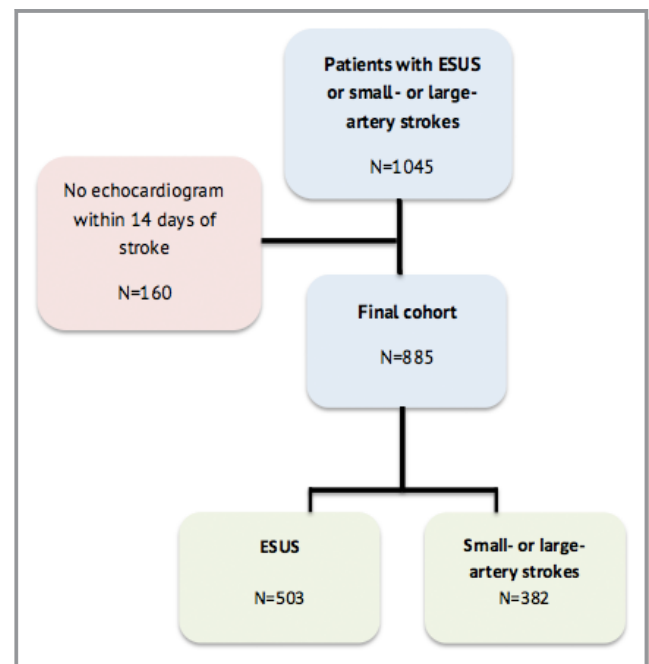


Figure. Flow-chart depicting cohort selection using the CAESAR (Cornell Acute Stroke Academic Registry). ESUS indicates embolic stroke of undetermined source.

attending cardiologist, and were defined as hypokinesia or akinesia of 1 or more wall segments in the absence of a recent (ie, within 4 weeks) myocardial infarction.

Given that ESUS likely represents a heterogeneous group of patients, in order to focus our study on ESUS patients who were likely to have a cardioembolic mechanism of stroke, in a secondary analysis we excluded cases of ESUS which did not meet the TOAST definition of large-artery atherosclerosis (>50% ipsilateral stenosis), but had any evidence of ipsilateral carotid atherosclerosis. A single neuroradiologist (A.G.) interpreted the imaging studies without knowledge of clinical data.

In order to account for potentially confounding factors between LVEF/LV wall motion abnormality and stroke subtype, we measured the following demographic stroke risk factors: age, sex, race, hypertension, dyslipidemia, diabetes mellitus, coronary artery disease (as defined by history of myocardial infarction or angina, or previous percutaneous coronary intervention), peripheral vascular disease, chronic kidney disease, tobacco use, alcohol or drug abuse, and previous stroke.

Confirmatory Cohort Analysis

We performed a confirmatory analysis among an external cohort of patients with acute ischemic stroke admitted to Rhode Island Hospital between January 1, 2016, and June 30, 2017. These data were collected in a Research Electronic Data Capture database (REDCap) as part of an institutional quality improvement project; institutional review board approval was obtained. For these data, stroke subtypes entered into REDCap are routinely verified by a second vascular neurologist (S.Y.), and in cases of disagreement, 2 vascular neurologists convene to arrive at consensus.⁸

Statistical Analysis

We used descriptive statistics with exact CIs to evaluate patient characteristics. We used the *t* test to compare LVEF, which was normally distributed, in patients with ESUS versus those with small- or large-artery strokes. We also used multiple logistic regression models to evaluate the association between LVEF and ESUS while adjusting for age, sex, race, hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, peripheral vascular disease, chronic kidney disease, tobacco use, alcohol or drug abuse, and previous stroke. In a sensitivity analysis, we excluded patients who were found to have atrial fibrillation on postdischarge prolonged cardiac rhythm monitoring. Additionally, in an exploratory analysis, we used the rank-sum test to evaluate the association between quartiles of LVEF and ESUS. We also evaluated the association between LVEF in patients with ESUS and small- and large-artery strokes after excluding patients with preserved LVEF (ejection fraction [EF] \geq 50%).

We used the chi-squared test to compare LV wall motion abnormality in patients with ESUS versus those with small- or large-artery strokes. We also used multiple logistic regression models to evaluate the association between LV wall motion abnormality and ESUS while adjusting for age, sex, race, hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, peripheral vascular disease, chronic kidney disease, tobacco use, alcohol or drug abuse, and previous stroke. All statistical analyses were performed by S.L.R. and A.E.M. using Stata/MP (version 13; StataCorp LP, College Station, TX). The threshold for statistical significance was $\alpha=0.05$.

Results

Among the 885 patients with ESUS or small- or large-artery strokes, mean age was 67.8 ± 15.0 years and 431 (48.7%) were women. Compared to patients with small- or large-artery strokes, patients with ESUS were younger, more often women, less often had hypertension, dyslipidemia, diabetes mellitus, prior stroke, or active tobacco use (Table 1).

Among the entire CAESAR cohort, mean LVEF was 62.3% ($\pm 7.9\%$) and median LVEF was 63.0% (interquartile range, 57.2–67.0). In univariate analysis, there was no difference in LVEF between patients with ESUS (62.4%; 95% CI, 61.7–63.0) and patients with small- or large-artery strokes (62.3%; 95% CI, 61.4–63.2; $P=0.9$). After adjustment for age, sex, race, hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, peripheral vascular disease, chronic kidney disease, tobacco use, alcohol or drug abuse, and previous stroke, there was no association between LVEF and ESUS (odds ratio [OR] per 5% decrement in EF, 1.0; 95% CI, 1.0–1.1; $P=0.6$; Table 2). Our results were unchanged after excluding patients found to have atrial fibrillation on postdischarge cardiac rhythm monitoring (OR per 5% decrement in EF, 1.0; 95% CI, 0.9–1.1; $P=0.5$).

In an exploratory analysis, quartiles of LVEF were not associated with ESUS (P value for comparison among groups=0.8). This lack of association persisted after comparing only the lowest and highest quartiles of LVEF ($P=0.8$). When we restricted our cohort to patients with an LVEF <50%, LVEF remained similar between patients with ESUS and those with small- or large-artery strokes after adjustment for age, sex, race, hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, peripheral vascular disease, chronic kidney disease, tobacco use, alcohol or drug abuse, and previous stroke (OR per 5% decrement in EF, 1.4; 95% CI, 0.7–2.9; $P=0.4$).

There were 52 patients (5.9%) with echocardiographic evidence of LV wall motion abnormality. Frequency of LV wall motion abnormality did not differ between patients with ESUS and those with small- or large-artery strokes (5.7% versus 6.0%; $P=0.9$). After adjustment for age, sex, race, hypertension,

Table 1. Characteristics of Acute Ischemic Stroke Patients, Stratified by Stroke Subtype

Characteristic*	ESUS (N=503)	Small- or Large-Artery Strokes (N=382)	P Value
Age, y, mean (SD)	66.2 (16.4)	70.0 (12.6)	<0.001
Female	274 (54)	157 (41)	<0.001
Race			0.18
White	427 (85)	318 (83)	
Black	46 (9)	30 (8)	
Hispanic	2 (0)	6 (2)	
Other	28 (6)	28 (7)	
Payment source			0.007
Medicare	174 (35)	145 (38)	
Medicaid	57 (11)	69 (18)	
Commercial	260 (52)	159 (42)	
Other	12 (2)	9 (2)	
Hypertension	296 (59)	299 (78)	<0.001
Diabetes mellitus	108 (21)	128 (34)	<0.001
Coronary artery disease	63 (13)	61 (16)	0.14
Peripheral vascular disease	19 (4)	15 (4)	0.91
Dyslipidemia	221 (44)	198 (52)	0.02
Chronic kidney disease	15 (3)	11 (3)	0.93
Previous stroke	84 (17)	90 (24)	0.01
Tobacco use	31 (7)	55 (14)	<0.001
Drug or alcohol abuse	4 (1)	7 (2)	0.17

ESUS indicates embolic stroke of undetermined source.

*Data are presented as number (%), unless otherwise specified.

dyslipidemia, diabetes mellitus, coronary artery disease, peripheral vascular disease, chronic kidney disease, tobacco use, alcohol or drug abuse, and previous stroke, there was still no association between LV wall motion abnormality and ESUS (OR, 0.9; 95% CI, 0.5–1.6; $P=0.7$; Table 2).

Among the confirmatory Rhode Island Hospital cohort, we identified 634 patients, among whom 388 (61%) had ESUS and 246 (39%) had small- or large-artery strokes. There was no difference in LVEF between patients with ESUS and those with small- or large-artery strokes after adjustment for age, sex, race, hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, peripheral vascular disease, chronic kidney disease, tobacco use, alcohol or drug abuse, and previous stroke (OR per 5% decrement in EF, 1.1; 95% CI, 1.0–1.2; $P=0.2$). In addition, there was no association between LV wall motion abnormality and ESUS after adjustment for age, sex, race, hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, peripheral vascular disease, chronic

Table 2. Relationship Between LVEF, LV Wall Motion Abnormality, and ESUS

	Odds Ratio	95% CI	P Value
Primary analysis*			
LVEF and ESUS	1.0 [†]	1.0 to 1.1	0.6
LV wall motion abnormality and ESUS	0.9	0.5 to 1.6	0.7
Secondary analysis[‡]			
LVEF and ESUS	1.2 [†]	1.0 to 1.5	0.04
LV wall motion abnormality and ESUS	1.6	0.4 to 6.5	0.5

ESUS indicates embolic strokes of undetermined source; LV, left ventricular; LVEF, left ventricular ejection fraction.

*Includes all patients with ESUS. Models are adjusted for age, sex, race, hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, chronic kidney disease, previous stroke, peripheral vascular disease, tobacco use, and drug and alcohol abuse.

[†]Per 5% decrement in LVEF.

[‡]Excludes patients with ESUS with evidence of ipsilateral carotid atherosclerosis. Models are adjusted for age, sex, race, hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, chronic kidney disease, previous stroke, peripheral vascular disease, tobacco use, and drug and alcohol abuse.

kidney disease, tobacco use, alcohol or drug abuse, and previous stroke (OR 1.2; 95% CI, 0.7–2.2; $P=0.5$).

In our secondary analysis, we restricted the cohort of ESUS patients to those without any evidence of ipsilateral carotid atherosclerosis and found an association between LVEF and ESUS after adjustment for age, sex, race, hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, peripheral vascular disease, chronic kidney disease, tobacco use, alcohol or drug abuse, and previous stroke (OR per 5% decrement in LVEF, 1.2; 95% CI, 1.0–1.5; $P=0.04$; Table 2). There remained no difference in the frequency of LV wall motion abnormality between patients with ESUS and those with small- or large-artery strokes (6.3% versus 4.8%; $P=0.6$; Table 2).

Discussion

Among patients in a prospective stroke registry, we found no difference in LVEF or presence of LV wall motion abnormality in all patients with ESUS as compared with patients with small- or large-artery strokes. However, when we excluded ESUS patients with any evidence of ipsilateral carotid atherosclerosis, lower LVEF appeared to be associated with ESUS.

Identification of severely depressed LVEF ($\leq 35\%$) is associated with an increased risk of stroke and may lead to changes in antithrombotic therapy.^{9,10} However, few studies have evaluated whether a more-modest reduction in LVEF increases stroke risk. Limited data suggest that even a

modest reduction in LVEF may serve as a nidus for LV thrombus formation and, as a consequence, an increased risk of embolic stroke.^{11,12} Our results suggest that among the entire population of ESUS, LVEF does not differ between patients with ESUS and patients with small- or large-artery strokes. However, the positive association between lower LVEF and ESUS found in our secondary analysis supports the notion that nonseverely (<35%) reduced LVEF may be a risk factor for stroke and that ESUS likely represents a heterogeneous group of patients—those with cardioembolic sources of embolism and those with nonstenosing atherosclerosis that do not meet the TOAST definition of large-artery atherosclerosis. Given that 2 recent trials failed to show a benefit of using anticoagulation in all patients with ESUS,^{13,14} our results add further credence to redefining the definition of ESUS into patients with a likely (1) cardioembolic mechanism of stroke, which may respond to anticoagulation, and (2) large-artery mechanism of stroke, which may be less likely to respond to anticoagulation.

Previous studies have found conflicting evidence regarding whether LV wall motion abnormality, in the absence of recent myocardial infarction, may be associated with an increased stroke risk.^{4,6,7} One recent study in Korea found that LV wall motion abnormality was independently associated with an elevated risk of recurrent stroke.¹⁵ However, although LV wall motion abnormality may allow for stasis and subsequent clot formation,^{16,17} we did not find an association between LV wall motion abnormality and ESUS in our study regardless of whether we excluded ESUS patients with mild-to-moderate ipsilateral stenosis. This lack of association held true upon adjusting for multiple confounding variables and in an external confirmatory cohort.

This study has several limitations. First, we excluded patients who did not undergo echocardiography within 14 days of acute ischemic stroke, which could have introduced selection bias. Second, we collected LVEF measurements from either transthoracic or transesophageal echocardiograms, which may have introduced measurement bias. However, past data suggest that echocardiography measurements of LVEF are comparable between transthoracic and transesophageal echocardiograms.¹⁸ Third, because the results of our study are based on patients admitted to a large tertiary-care hospital, our results may not generalize to other ischemic stroke populations; however, our results were similar at another tertiary care center.

Conclusions

We found no difference in LVEF and LV wall motion abnormality among all patients with ESUS and small- or large-artery strokes. However, when we excluded ESUS patients with any evidence of ipsilateral carotid atherosclerosis,

we found an association between lower LVEF and ESUS. These results suggest that nonseverely (<35%) reduced LVEF may be a risk factor for ESUS. Furthermore, our data suggest that the definition of ESUS should be revisited and perhaps ESUS cases should be divided into those with a likely cardioembolic mechanism of stroke, which may respond to anticoagulation, and those with a likely noncardioembolic mechanism of stroke, such as mild-to-moderate atherosclerotic disease, which may be less likely to respond to anticoagulation.

Sources of Funding

Dr Navi is supported by NIH grant K23NS091395 and the Florence Gould Endowment for Discovery in Stroke. Dr Kamel is supported by NIH/NINDS grants R01NS097443 and U01NS095869. Dr Merkler is supported by the American Heart Association grant 18CDA34110419, NIH grant KL2TR0002385, and the Leon Levy Foundation in Neuroscience.

Disclosures

None.

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