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Short-Term Risk of Ischemic Stroke after Detection of Left Ventricular Thrombus on Cardiac MRI

Alexander E. Merkler, MD[1,2], **Javid Alakbarli, MD**[3], **Gino Gialdini, MD**[2], **Babak B. Navi, MD, MS**[1,2], **Santosh B. Murthy, MD, MPH**[1,2], **Parag Goyal, MD, MSc**[3], **Jiwon Kim, MD**[3], **Richard B. Devereux, MD**[3], **Monika M. Safford, MD**[3], **Costantino Iadecola, MD**[1,2], **Hooman Kamel, MD**[1,2], **Jonathan W. Weinsaft, MD**[3]

[1]Department of Neurology, Feil Family Brain and Mind Research Institute, Weill Cornell Medicine, New York, NY

[2]Clinical and Translational Neuroscience Unit, Feil Family Brain and Mind Research Institute, Weill Cornell Medicine, New York, NY

[3]Department of Medicine, Weill Cornell Medicine, New York, NY

Abstract

Background: The short-term risk of ischemic stroke in patients with left ventricular (LV) thrombus identified via delayed-enhancement cardiac magnetic resonance (DE-CMR) imaging is uncertain.

Methods: We performed a retrospective cohort study of patients who underwent DE-CMR for evaluation of LV systolic dysfunction at NewYork-Presbyterian Hospital/Weill Cornell between 2007-2016. We identified all hospitalized patients who had DE-CMR evidence of LV thrombus, and as controls, all hospitalized patients who had no DE-CMR evidence of LV thrombus; two control patients were randomly selected for each patient with LV thrombus. Our primary outcome was ischemic stroke prior to hospital discharge. Additionally, we compared the risk of stroke among patients with: (1) no LV thrombus, (2) LV thrombus by DE-CMR but not by echocardiography, and (3) LV thrombus by both DE-CMR and echocardiography.

Results: We identified 33 patients with LV thrombus and 66 patients without LV thrombus on DE-CMR. Of the 33 patients with LV thrombus on DE-CMR, 13 had echocardiographic evidence of thrombus. Ischemic stroke occurred in 3 of 33 (9.1%; 95% CI, 1.9-24.3%) patients with LV thrombus on DE-CMR. Ischemic stroke occurred in 0 of 66 (0%; 95% CI, 0-5.4%) patients without LV thrombus on DE-CMR, 1 of 20 (5.0%; 95% CI, 0.1-24.9%) patients with thrombus on

Corresponding Author: Alexander E. Merkler, MD, Department of Neurology, Weill Cornell Medicine, 525 East 68th Street, F610, New York, NY 10065, Tel: 212-746-0225, Fax: 212-746-5509, alm9097@med.cornell.edu.

Declaration of Conflicting Interests

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DE-CMR but not echocardiogram, and 2 of 13 (15.4%; 95% CI, 1.9-45.4%) patients with thrombus on both DE-CMR and echocardiogram (*P* value for comparison among groups, 0.02).

Conclusions: We found a 9% short-term risk of ischemic stroke in patients with LV thrombus detected on DE-CMR.

Keywords

Cerebrovascular disease/stroke; ischemic stroke; cardiomyopathy; myocardial infarction; left ventricular thrombus

Left ventricular (LV) thrombus is a potential complication of acute myocardial infarction or cardiomyopathy and carries a heightened risk of embolic phenomena including stroke.(1–6) Identification of LV thrombus in patients with myocardial infarction or cardiomyopathy is important because anticoagulation therapy reduces the risk of embolization.(6) Conventional transthoracic echocardiography is widely accepted as the primary screening test for cardiac function, structure and identification of LV thrombus.(7,8) However, echocardiography detects LV thrombus based upon anatomic appearance – an approach that can be suboptimal when LV thrombi are small, or image quality is poor. Delayed-enhancement cardiac magnetic resonance (DE-CMR) imaging enables LV thrombus identification based on intrinsic tissue properties stemming from avascular composition.(1,9) Prior research has shown CMR tissue characterization to yield improved LV thrombus detection compared to anatomic imaging via echocardiography and other modalities.(1,2,10) Moreover, DE-CMR imaging has been validated as a highly reliable test for pathology-evidenced LV thrombus with a sensitivity and specificity superior to that of conventional echocardiography.(1,2,10) However, the risk of ischemic stroke in patients with LV thrombus identified on DE-CMR is uncertain. We therefore evaluated the risk of ischemic stroke in patients with LV thrombus identified via DE-CMR among hospitalized patients undergoing DE-CMR imaging for the evaluation of LV systolic dysfunction.

Materials and Methods

Design

We performed a retrospective cohort study of patients who underwent DE-CMR imaging for inpatient evaluation of LV systolic dysfunction (ejection fraction <55%) between 2007-2016 at NewYork-Presbyterian Hospital/Weill Cornell Medical Center (NYPH/Cornell). Using an existing registry of all patients who underwent CMR imaging at NYPH/Cornell, we identified all hospitalized patients evaluated for LV systolic dysfunction who had DE-CMR imaging evidence of LV thrombus. Using the imaging registry, we created a control group of hospitalized patients who also underwent DE-CMR imaging for evaluation of LV systolic dysfunction but had no evidence of LV thrombus; using a random number generator, two control patients were randomly selected for each patient with DE-CMR evidence of LV thrombus. Patients who did not undergo conventional transthoracic echocardiography or who had contraindications to gadolinium contrast administration (e.g. glomerular filtration rate <30ml/min/1.73m^2) were excluded. Additionally, in order to focus on the risk of ischemic stroke after LV thrombus detection, we excluded patients with inpatient ischemic stroke that occurred prior to LV thrombus detection. The data and analytic methods of this study are

available upon request from the corresponding author. The Weill Cornell Medicine institutional review board approved this study and waived the requirement for informed consent.

Measurements

CMR imaging was performed using 1.5T or 3.0T commercial scanners. CMR without contrast (Cine-CMR) was performed using a steady-state free precession sequence. Gadolinium was then intravenously administered (0.2mmol/kg) to patients. DE-CMR was performed 10 minutes afterwards using a segmental inversion recovery sequence.(2) Cine- and DE-CMR images were acquired in matching planes. Short axis imaging was contiguous throughout the left ventricle. Long axis images were acquired in two-, three-, and four-chamber orientations.

Conventional transthoracic echocardiograms were performed using commercial equipment (General Electric Vivid-7 or Siemens Sequoia) by trained sonographers. Images were acquired in standard parasternal and apical imaging planes with at least three (two-, three-, four-chamber) apical orientations.

Presence or absence of LV thrombus was coded via review of pre-existing clinical CMR and echocardiography reports. LV thrombus was identified based on tissue properties as a discrete non-enhancing LV mass with characteristics consistent with avascular tissue (i.e. lack of enhancement on standard or long TI inversion recovery DE-CMR).(1,2) LV thrombus was diagnosed on conventional echocardiography based on morphology/mobility pattern, for which it was defined as a protuberant or independently mobile mass in the LV cavity distinguishable from papillary muscles, trabeculae, chordal structures, technical artifact, or tangential views of the LV wall.(2,10,11)

In addition to demographic variables, covariates included stroke risk factors and burden of myocardial infarct. Stroke risk factors were: hypertension, diabetes mellitus, atrial fibrillation, coronary artery disease, peripheral vascular disease, chronic kidney disease, chronic obstructive pulmonary disease, alcohol abuse, and tobacco use. As per prior studies, myocardial infarction was scored using a 17-segment model. Segmental function was graded on cine-CMR imaging (0=normal contraction; 1 = mild hypokinesia; 2 = moderate hypokinesia; 3 = severe hypokinesia; 4 = akinesia; 5 = dyskinesia). DE-CMR images were scored for infarct size based on transmural extent of hyperenhancement (0 = none; 1 = 1-25%; 2 = 25-50%; 3 = 51-75%; 4 = 76-100%). Global myocardial infarct burden was calculated by summing segmental scores weighted by the midpoint of the range of hyperenhancement and dividing by the total number of segments.(10,12)

Outcomes

Our primary outcome was ischemic stroke that occurred during the hospitalization in which DE-CMR was obtained. Additionally, we compared the risk of stroke prior to hospital discharge among three groups of patients: (1) those with no evidence of LV thrombus, (2) those with LV thrombus by DE-CMR but not by echocardiography, and (3) those with LV thrombus by both DE-CMR and echocardiography. The outcome of ischemic stroke was defined as the sudden onset of a neurological deficit without an obvious non-vascular cause

and with corresponding CT or magnetic resonance imaging evidence of infarction. One neurologist blinded to cardiac imaging findings (AEM) reviewed all charts for a clinical event consistent with ischemic stroke with corresponding imaging evidence of infarction.

Statistical Analysis

We used the Chi-square or Fisher's exact test for the analyses of categorical variables and the 2-tailed t-test or Mann-Whitney test for the analyses of continuous variables. Crude rates were reported using descriptive statistics with exact 95% confidence intervals. Statistical significance was set at a threshold of alpha = 0.05. All analyses were performed using Stata/MP version 14 (College Station, TX).

Results

We identified 33 patients with evidence of LV thrombus on DE-CMR and 66 patients without LV thrombus on DE-CMR. The mean age of patients with and without LV thrombus was similar (56.8 [±13.1] years versus 60.0 [±14.4] years). Individuals with LV thrombus on DE-CMR had a higher burden of myocardial infarct than individuals without LV thrombus (21.4% versus 8.3%, $P<0.001$), but had similar ejection fractions (28.8% versus 31.1%, $P=0.34$) and a similar number of medical comorbidities (Table 1).

The median time from echocardiography to DE-CMR imaging was 2 days (interquartile range, 1-4 days). Among the 33 patients with LV thrombus on DE-CMR, 13 (39%) also had concordant evidence of LV thrombus on conventional transthoracic echocardiography. An additional 4 patients with DE-CMR evidence of LV thrombus underwent adjunctive testing via contrast echocardiography, among whom 2 had evidence of LV thrombus. Finally, 2 patients with DE-CMR evidence of LV thrombus underwent transesophageal echocardiography, among whom 1 had evidence of LV thrombus (this patient was also identified as having a LV thrombus on contrast echocardiography). No patient without DE-CMR evidence of LV thrombus had a LV thrombus identified on echocardiography. Nearly all patients (30/33, 90.9%; 95% confidence interval [CI], 75.7-98.1%) were started on anticoagulation therapy after LV thrombus identification. Anticoagulation was started within 24 hours of discovery of LV thrombus in all but 1 patient. Of the 30 patients treated with therapeutic anticoagulation, 22 were initially treated with unfractionated intravenous heparin, 7 with low molecular weight heparin (Enoxaparin), and one with warfarin. All patients receiving unfractionated intravenous heparin were being given treatment doses based on a standardized institutional nomogram. Enoxaparin was given subcutaneously using a twice daily (1mg/kg) dosing regimen.

Ischemic stroke prior to hospital discharge occurred in 3 of 33 (9.1%; 95% CI, 1.9-24.3%) patients with LV thrombus detected on DE-CMR. Ischemic stroke occurred in 0 of 66 (0%; 95 CI, 0-5.4%) patients without LV thrombus on DE-CMR, 1 of 20 (5%; 95% CI, 0.1-24.9%) patients with LV thrombus on DE-CMR but not echocardiogram, and 2 of 13 (15.4%; 95% CI, 1.9-45.4%) patients with LV thrombus by both DE-CMR and echocardiography (P value for comparison among groups, 0.02) (Table 2). Neither of the 2 patients who were found to have LV thrombus on contrast echocardiography had an ischemic stroke. All patients who developed an ischemic stroke were started on

anticoagulation therapy the day of LV thrombus discovery. In addition, all three patients who developed an ischemic stroke were being treated with unfractionated intravenous heparin and had a PTT within the therapeutic range at the time of stroke.

Discussion

We found that among inpatients who underwent DE-CMR imaging for evaluation of LV systolic dysfunction, there was an approximately 9% short-term risk of ischemic stroke when LV thrombus was detected, despite the use of anticoagulation in 90% of patients.

Currently, uncertainty remains regarding the optimal screening pathway, antithrombotic treatment regimen and treatment duration for patients with LV systolic dysfunction.(13) The WARCEF study found that among patients with reduced ejection fraction but without atrial fibrillation, warfarin reduced the risk of ischemic stroke, but this benefit was offset but an increased risk of intracerebral hemorrhage.(14) To date, no randomized trial has been performed evaluating contemporary antithrombotic therapy regimens aimed at preventing LV thrombus formation among patients with LV systolic dysfunction. Furthermore, even in the setting of LV thrombus discovery, prospective data on the best antithrombotic treatment regimen and duration are lacking.

Conventional transthoracic echocardiography is widely accepted as the primary screening test for detecting LV thrombus, but its sensitivity for this is low.(1,7,8) CMR is a relatively novel but highly reproducible imaging modality for evaluating cardiac structure, function, perfusion, and tissue characterization.(2,7) Prior studies have demonstrated a high risk of embolic phenomena, including stroke, in patients with LV thrombus identified via echocardiography.(2–6) Our results build upon these findings by elucidating the short-term risk of ischemic stroke in patients with LV thrombus identified on DE-CMR. In addition, our results suggest that patients with LV thrombus identified on DE-CMR but not echocardiography are at risk for ischemic stroke. Furthermore, although CMR imaging is not currently recommended in the evaluation of ischemic stroke, prior studies have demonstrated that CMR is feasible in stroke patients and that the rate of LV thrombus detection is significantly higher using DE-CMR as compared to conventional echocardiography.(15–17) Increased utilization of DE-CMR as a screening tool for LV thrombus may lead to advances in the management of patients with LV systolic dysfunction as improved LV thrombus detection may lead to an increased use of anticoagulation therapy and, as a consequence, a decreased incidence of ischemic stroke.

The results of our study must be considered in light of its limitations. First, the sample size is small with few outcome events and wide confidence intervals. Second, given the modest number of patients, we were unable to adjust for demographics and cardiovascular risk factors. Third, most patients only underwent conventional echocardiography; since echocardiography with contrast is superior to conventional echocardiography at detecting LV thrombus,(18) it is likely that the incremental yield of detecting LV thrombus on DE-CMR as compared to contrast echocardiography is lower. However, as LV thrombus is rarely the primary indication for echocardiography, most patients undergoing echocardiography for screening of cardiac structure and function will not receive contrast.(8) Fourth, although

both echocardiography and DE-CMR were performed within the same hospitalization, DE-CMR was performed a median of 2 days after the echocardiography, thus conceivably allowing for the potential formation of LV thrombus in the interim. Fifth, we only evaluated the risk of ischemic stroke prior to hospital discharge. Further studies will be necessary to determine the long-term risk of ischemic stroke in patients with LV thrombus detected on DE-CMR.

Among inpatients who had DE-CMR for the evaluation of LV systolic dysfunction, there was a nearly 10% short-term risk of acute ischemic stroke when LV thrombus was identified, despite the use of therapeutic anticoagulation in nearly all patients. Further studies are needed to obtain more robust estimates of the short-term risk of ischemic stroke and to elucidate the long-term risk of ischemic stroke among patients with LV thrombus identified on DE-CMR.

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Table 1.

Characteristics of Patients Stratified by LV Thrombus on DE-CMR

Characteristic*	LV Thrombus (N = 33)	No LV Thrombus (N = 66)	P value
Age, mean (SD), y	56.8 (13.1)	60.0 (14.4)	0.29
Female	7 (21.2)	22 (33.3)	0.21
Hypertension	17 (51.5)	42 (63.6)	0.25
Hyperlipidemia	14 (42.4)	34 (51.5)	0.39
Diabetes	11 (33.3)	18 (27.3)	0.53
Coronary artery disease	21 (63.6)	40 (60.6)	0.77
Ejection Fraction, % (SD)	28.8 (12.6)	31.1 (10.2)	0.33
Myocardial infarct burden (SD)†	21.5 (13.0)	8.3 (12.9)	<0.001
Peripheral vascular disease	2 (6.1)	5 (7.6)	1.00
Chronic obstructive pulmonary disease	2 (6.1)	5 (7.6)	1.00
Chronic kidney disease	7 (21.2)	6 (9.1)	0.09
Atrial fibrillation	2 (6.1)	12 (18.2)	0.13
Prior Stroke	0 (0)	6 (6.3)	0.17
Tobacco use	7 (21.2)	16 (24.2)	0.74

Abbreviations: LV, left ventricular; DE-CMR, delayed-enhancement cardiac magnetic resonance imaging; SD, standard deviation.

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

†Calculated as global myocardial infarct size on DE-CMR.

Table 2.

Rate of Ischemic Stroke Prior to Discharge in Patients undergoing DE-CMR

	No LV Thrombus on DE-CMR or TTE	LV Thrombus on DE-CMR but not TTE	LV Thrombus on DE-CMR and TTE
Stroke	0 (0)	1 (5)	2 (15.4)
No Stroke	66 (100)	19 (95)	11 (84.6)

Abbreviations: LV, left ventricular; DE-CMR, delayed-enhancement cardiac magnetic resonance imaging; TTE, transthoracic echocardiogram without contrast.

Data are presented as number (%).