Journal of the American Heart Association

ORIGINAL RESEARCH

The Investigation of Left Atrial Structure and Stroke Etiology: The I-LASER Study

Michelle C. Johansen, MD, PhD; Henrique Doria de Vasconcellos, MD; Saman Nazarian, MD, PhD; Joao A. C. Lima, MD, MBA; Rebecca F. Gottesman, MD, PhD

BACKGROUND: Left atrial (LA) function is important in stroke, but often poorly characterized. We evaluated the association of 2-dimensional speckle tracking echocardiography LA variables with stroke subtype (cardioembolic stroke [CS] *or* cryptogenic stroke versus other). The hypothesis is worse LA active function is associated with CS, but not cryptogenic strokes.

METHODS AND RESULTS: In this prospective cohort (2017–2019), left ventricular/LA structure and function were quantified by 2-dimensional and speckle tracking echocardiography in 151 patients with stroke. Strain/strain rate curves for the 3 components of the LA cycle, ie, (1) Reservoir (global longitudinal strain [Srmax]), (2) Conductive (early LA Sr [Sre]), and (3) Active (late LA strain [Sra]) were evaluated, masked to stroke subtype. Associations of cardiac features with stroke subtype were tested using multivariable logistic regressions. Odds of CS were increased in patients with a larger LA systolic diameter (odds ratio [OR], 2.96, 95% CI, 1.14–7.69) but reduced in patients with a higher Srmax (better reservoir) (OR, 0.80, 95% CI, 0.67–0.97). Lower Sra (worse function) was associated with an increased odds of CS (OR, 1.72, 95% CI, 1.07–2.76) but not independent of atrial fibrillation. Higher active LA emptying fraction (better active phase) was associated with reduced odds of CS (OR, 0.74, 95% CI, 0.57–0.95) or cryptogenic stroke (OR, 0.82, 95% CI, 0.68–0.98) versus other subtypes; other associations between cryptogenic stroke and speckle tracking echocardiography were not found.

CONCLUSIONS: Markers of LA structure and function were associated with CS. Similar associations were not found for cryptogenic stroke, which might suggest different underlying mechanisms, given study limitations. Further understanding could aid stroke diagnosis and secondary stroke prevention research.

Key Words: arrhythmia ■ brain ischemia ■ echocardiography ■ left atrium ■ stroke

Although treatment guidelines for atrial tachyarrhythmias, such as atrial fibrillation (AF), are established, the role of other alterations in left atrial (LA) structure and function is unclear. Atrial tachyarrhythmia is suggested to be a symptom of underlying atrial substrate disease ("atrial myopathy") and this concept has gained increasing acceptance.[1-3]

While there are no standard guidelines for cardiovascular evaluation of a patient with acute stroke,[4] transthoracic echocardiogram (TTE) is widely performed as the initial test. This method, however, without further image analysis, does not adequately measure cardiac strain. Strain may capture subtle abnormalities in LA function not otherwise appreciated on standard transesophageal echocardiography sequences. Strain is defined as deformation of an object normalized to its original shape and size, with positive values representing stretch, and negative values shortening. The use of speckle-tracking techniques, which leverages acoustic markers in the echo images to evaluate any local myocardial deformations, easily allows quantification of myocardial strain.[5] Speckle-tracking echocardiography (STE) can be performed using TTE images and is a valid approach to assess LA structure and function.[6]

We aim to utilize clinically obtained TTE in patients with ischemic stroke, and apply STE methods in order to identify important LA structural and functional variables and to determine the association of these

Correspondence to: Michelle C. Johansen, MD, PhD, 600 N. Wolfe St, Phipps 4 Suite 446, Baltimore, MD 21287. E-mail: mjohans3@jhmi.edu

Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.018766

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Although treatment guidelines for atrial tachyarrhythmias, such as atrial fibrillation, are established, the role of other alterations in left atrial (LA) structure and function is unclear among patients with ischemic stroke.
- Our study uniquely considered LA strain analysis, a noninvasive echocardiography method by which to garner information about the phasic function of the LA, and its relationship with stroke subtype.

What Are the Clinical Implications?

- Larger LA volumes, better LA reservoir function, and worse LA active function are associated with cardioembolic stroke, specifically confirming the hypothesis that worse LA function would be associated with cardioembolic stroke compared with all other stroke subtypes.
- When considering cryptogenic strokes, or strokes of unknown cause, the associations were not consistent, suggesting that this is a diverse group, with heterogeneous stroke mechanisms.
- LA strain coupled with more advanced imaging techniques, or a combination of biomarkers, could help in the future to improve separation of patients who may have an underlying cardiac cause versus other possible mechanisms.

Nonstandard Abbreviations and Acronyms

LA	left atrial
STE	speckle-tracking echocardiography
TTE	transthoracic echocardiogram

variables with stroke subtype, with a focus on both cardioembolic stroke as well as stroke of unknown cause (also called cryptogenic stroke), compared with other stroke subtypes.

METHODS

This study was conducted at a single center, the Johns Hopkins Hospital, which is a comprehensive tertiary referral center for stroke. This study was approved by the Institutional Review board and all patients gave written informed consent. Anonymized data will be shared by request from qualified investigators. Inclusion criteria for the study were adult patients (≥21 years of age) admitted consecutively to Johns Hopkins Hospital (2017–2019) with an acute ischemic stroke with confirmatory cerebral magnetic resonance imaging and a clinical indication for a TTE.

Echocardiography Assessment

TTE was obtained at the discretion of the inpatient treatment team as was standard practice at the time of study enrollment. Two-dimensional echocardiography was performed by certified sonographers following standardized protocol based on the American Society of Echocardiography guidelines.[7] Patients were examined in a left lateral decubitus position, utilizing parasternal long axis, parasternal short axis, apical 4-chamber, apical 2-chambers, and apical 3-chambers traditional views. ECG tracing was recorded during the examination. All recording and measurements were done at the end-expiration, with a full 3-cardiac cycle capture. Because the TTEs were clinically indicated and not research protocol, the number of observations for each of the variables of interest differs as a result of the different protocols reflective of the clinical indication. Two-dimensional echocardiography left ventricle (LV) characteristics were also obtained because of its relevance in LA dynamics because of pressure load.

Two-Dimensional Echocardiography and LA Speckle Tracking Acquisition and Analysis

A phased array transductor was used to acquire the 2-dimensional echocardiography tissue harmonic imaging, color Doppler, pulse-wave Doppler, and continuous-wave Doppler. The LA structure and function analysis were made offline by a certified, trained reader using a wall motion tracking software package (Image Arena Version 4.6, TomTec Imaging System) in both 2- and 4-chamber views.

The LA volumes, strain, and strain rate measures were defined as per the Figure. The 3 emptying fractions (total, passive, and active) were calculated based on the LA volumes (Data S1). Three emptying fractions (total, passive, and active) were calculated based on those volumes. Additional details are provided in Data S1.

Stroke Subtype

Stroke subtype was adjudicated according to TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria by a cerebrovascular neurologist who was masked to the echo features. Ten percent of the cases were re-adjudicated by another masked cerebrovascular neurologist with excellent interrater reliability (89%). All additional information including brain magnetic resonance imaging, admission and progress notes, and discharge summaries were used in stroke adjudication.

The TOAST classification[8] denotes 5 subtypes of ischemic stroke: (1) large-artery atherosclerosis, (2) cardioembolism or cardioembolic stroke, (3) small-vessel occlusion, (4) stroke of other determined cause, and (5) stroke of undetermined cause, and was chosen because it is one of the most widely used classification systems.

Covariates

Age, sex, race (Black versus other), body mass index (kg/m^2), hemoglobin A1C (%), low-density lipoprotein (LDL; mg/dL), systolic blood pressure on admission (mm Hg), and smoking status (ever versus never) were covariates of interest. A patient-reported history of AF or any prior documentation of a diagnosis of AF at the time of admission was used as diagnostic of AF. Inpatient ECG, telemetry, or postdischarge cardiac event monitors when available were also considered. The decision about placing an implantable loop recorder or discharging the patient with a cardiac event monitor was made by the clinical team, who was not aware of the study hypotheses.

Statistical Analysis

The primary dependent variables, in separate analyses, were stroke subtype, specifically either cardioembolic stroke (versus all others), or stroke of unknown cause (versus other, not including cardioembolic stroke). Separate multivariable logistic models were constructed with nested adjustment models for both analyses. Covariates that, based on prior literature, might be important confounders of the proposed associations, were included in the multivariable models. Model 1 adjusted for participant age, sex, and race (Black versus other). Model 2 adjusted for Model 1 and body mass index, LDL, hemoglobin A1C, admission systolic blood pressure, and current smoking. Model 3 adjusted for Model 2 and diagnosis of AF. Models considered each echo variable, as independent variables, separately. LV ejection fraction (LVEF) was also dichotomized at 55% because this is the cutoff of normal LVEF for women according to established criteria.[7] A sensitivity analysis was performed excluding participants who had AF, rather than adjusting for AF as a confounder because it is possible that AF is on the causal pathway between the TTE variables and stroke cause (specifically, cardioembolic stroke as the dependent variable). Additionally, an interaction term was included in the whole cohort to evaluate for effect measure modification by AF. A third sensitivity analysis was performed excluding patients with cryptogenic stroke when the primary dependent variable was cardioembolic stroke (Data S1). This was done in the event that the pathophysiology of cryptogenic stroke might be too heterogeneous to include in the comparator group. Because of the potential for multiple comparisons given multiple cardiac measures being evaluated, we also present Bonferroni-corrected results for the 2 primary analyses. All statistical analyses were performed using Stata v14.1.[9] Two-sided $P<0.05$ was considered statistically significant.

RESULTS

Demographics

One hundred sixty-three patients met inclusion criteria and provided informed consent. Of these, 4 were discharged before the TTE was obtained, 2 participants had limited TTEs secondary to the study being aborted, and 6 participants did not have complete demographic data. Baseline demographics for the remaining 151 patients are provided (Table 1). Twenty-nine participants (19%) had an ejection fraction <55%. Twenty-seven participants were adjudicated as having cardioembolic stroke, 34 as large artery atherosclerosis, 40 as small vessel disease, 14 with stroke of other causes, and 36 participants with stroke of unknown cause (32 with competing causes, 3 with a negative workup, 1 incomplete evaluation). Patients with a stroke of unknown cause had a statistically significant lower mean LDL (88.4 mg/dL versus 108 mg/dL), but otherwise had demographics similar to those with strokes of other subtypes. Of the 27 participants adjudicated as having cardioembolic stroke, 15 had or were diagnosed with AF (29 participants total had AF). National Institutes of Health Stroke Scale ranged from 0 to 28, but the majority of the participants had milder strokes, with 69% having a National Institutes of Health Stroke Scale ≤5.

Associations of LA Volumes and LA Strain With Cardioembolic Stroke

A larger LA maximal systolic diameter was associated with approximately a 3 times higher odds of

Table 1. Characteristics of the Patients at Baseline (N=151)*

Age, y	61 (14)
Female sex, n (%)	86 (57)
Black race, n (%)	88 (58)
Body mass index, kg/m^2	29.0 (7.0)
Hemoglobin A1C, %	6.3 (1.8)
Low-density lipoprotein, mg/dL	103.4 (42.5)
Systolic blood pressure, mm Hg	151.4 (32.3)
Smoker, n (%)	84 (56)
History of atrial fibrillation, n (%)	29 (19%)

*All values are mean (SD) unless otherwise noted. Smoker defined as ever vs never smoker.

cardioembolic stroke (odds ratio [OR] 2.96, 95% CI, 1.14–7.69; Model 3; Table 2). Similarly, participants with larger LA volumes (left atrial maximum volume, left atrial minimum volume) had a 4% increased odds of cardioembolic stroke, but this lost significance after adjusting for AF (Model 2).

A low absolute value of late negative peak strain rate (late left atrial strain rate), which reflects worse LA active phase, was significantly associated with an increased odds of cardioembolic stroke in the first 2 adjustment models (OR, 1.72, 95% CI, 1.07–2.76, Model 2) but lost significance after adjusting for AF. An increase or improvement in active LA emptying fraction (per 5%) was significantly associated with a decreased odds of cardioembolic stroke in the final model (OR, 0.74, 95% CI, 0.57–0.95). A higher maximum LA global longitudinal strain (per 5%), which reflects better LA reservoir function, was associated with a 32% reduction in the odds of cardioembolic stroke in the final adjustment model (95% CI, 0.52–0.90), a finding that was mirrored by the other 2 strain markers of reservoir LA function. Both a unit increase in systolic peak strain rate, indicative of better LA function (OR, 0.28, 95% CI, 0.08–0.95), and total LA emptying fraction (per 5%, OR, 0.80, 95% CI, 0.67–0.97) were associated with a decreased odds of cardioembolic stroke (Model 3). There were no significant associations found between cardioembolic stroke and variables indicative of LA conduit function. As noted in Table 2 by the asterisks, the majority of the findings maintain statistical significance when accounting for the possibility of multiple comparisons.

Associations of LV Structure and Cardiac Diastolic Function With Cardioembolic Stroke

Among those with a LVEF <55%, there were 4 times the odds of cardioembolic stroke (95% CI, 1.13–17.56, Model 3) compared with those with a normal LVEF. When considering LVEF as a continuous variable, an increase of 5% was associated with 34% lower odds of cardioembolic stroke in the final adjustment model (95% CI, 0.48–0.90). A larger LV end-diastolic diameter was associated with nearly 3 times the odds of cardioembolic stroke (95% CI, 1.17–6.20, Model 3). A larger LV end-diastolic or end-systolic volume (per 5 mL/m^2) was associated with cardioembolic stroke (OR, 1.12, 95% CI, 1.01–1.24; OR, 1.18, 95% CI, 1.01–1.37) but was no longer statistically significant after adjusting for additional risk factors and AF. A larger mitral E/A ratio, a marker of diastolic dysfunction, was associated with a higher odds of cardioembolic stroke in the final adjustment model (OR, 2.25, 95% CI, 1.25–4.06).

Sensitivity Analyses Both Excluding Participants With AF and Stratifying by AF

Participants with a larger LA maximum systolic diameter had 7 times the odds of cardioembolic stroke compared with those with diameters that were 1-cm smaller, with consideration given to the imprecision of the effect estimate with reduced power (95% CI, 1.41–38.31; Table 3). A higher active LA emptying fraction was associated with 49% lower odds of cardioembolic stroke among those without AF (95% CI, 0.30–0.88) and a higher total LA emptying fraction was associated with a 28% lower odds of cardioembolic stroke (95% CI, 0.56–0.92, Model 1) but was no longer significant after accounting for additional vascular risk factors. Excluding participants with AF did not change the lack of association with variables of LA conduit function. When considering the potential for an interaction of AF with the association between the cardiac variables and cardioembolic stroke, both LVEF (AF OR, 1.05, *P* value 0.86; without AF OR, 0.36, *P* value 0.007; *P*-interaction 0.03) and active LA emptying fraction (AF OR, 0.85, *P* value 0.41; without AF OR, 0.50, *P* value 0.009; *P*-interaction 0.01) had significant interaction terms (≤0.05). In both cases the effect estimate was significant and the protective association strengthened in the cohort without AF.

Sensitivity Analysis Excluding Participants With Cryptogenic Stroke

In general, excluding participants with cryptogenic stroke strengthened the effect estimates when considering the association between markers of LA volume, LA active and reservoir phase, and cardioembolic stroke (Table S1). For example, a 1-cm increase in LA diameter is associated with an OR of 5.29 (versus 2.96) in the final adjustment model in this restricted population, with some loss of precision (95% CI, 1.55–18.11). As anticipated, there were no significant associations found between cardioembolic stroke and variables indicative of LA conduit function. LV estimates became more unstable with loss of power.

Associations of Cardiac Variables With Stroke of Unknown Cause, or Cryptogenic Stroke

After excluding patients with adjudicated cardioembolic stroke (N=27) from the comparator group, the association of TTE cardiac variables with the outcome of stroke of unknown cause, or cryptogenic stroke, versus other noncardioembolic stroke, was analyzed (Table 4). Participants with larger left atrial maximum volume had a 3% higher odds of cryptogenic stroke (OR, 1.03, 95% CI, 1.001–1.06) but this finding was not consistent across the adjustment models. Participants

Table 2. Multivariable Logistic Regression of Cardiac Variables With Cardioembolic Stroke Subtype Versus Other Stroke Subtypes

Cardiac Variable	Number of Observations With Available Data	Univariate	95% CI	Model 1 OR	95% CI	Model 2 OR	95% CI	Model 3 OR	95% CI
LA volumes									
LA anteroposterior maximum systolic diameter, cm	149	2.81*,†	1.58–5.00	4.45*,†	2.17–9.16†	4.39*,†	1.92–10.02†	2.96†	1.14–7.69†
Maximum LA volume (LAVmax, mL/m^2)	146	1.03*,†	1.01–1.05†	1.04*,†	1.02–1.07†	1.04*,†	1.01–1.07†	1.02	0.98–1.05
Minimum LA volume (LAVmin, mL/m^2)	146	1.05*,†	1.02–1.07†	1.07*,†	1.04–1.11†	1.07*,†	1.03–1.11†	1.04	1.00–1.08
Pre-atrial contraction LA volume (LAVpre, mL/m^2)	129	1.01	0.98–1.04	1.03	0.99–1.06	1.02	0.99–1.06	1.01	0.96–1.05
LA active phase									
Late negative peak strain rate (LASra, s^{-1})	129	1.79*,†	1.15–2.80†	1.92*,†	1.22–5.45†	1.72†	1.07–2.76†	1.42	0.82–2.46
Active LA emptying fraction (per 5%)	132	0.71*,†	0.57–0.87†	0.68*,†	0.54–0.85†	0.71*,†	0.56–0.90†	0.74*,†	0.57–0.95†
LA conduit phase									
Early negative peak strain rate (LASre, s^{-1})	135	1.04	0.68–1.58	1.35	0.79–2.30	1.42	0.81–2.50	1.71	0.80–3.62
Passive LA emptying fraction (per 5%)	132	1.07	0.91–1.26	1.00	0.83–1.21	1.01	0.83–1.23	1.00	0.96–1.05
LA reservoir phase									
Maximum global longitudinal strain (LSmax, per 5%)	141	0.72*,†	0.59–0.88†	0.64*,†	0.50–0.80†	0.64*,†	0.50–0.82†	0.68*,†	0.52–0.90†
Systolic peak strain rate, s^{-1}	141	0.27*,†	0.11–0.69†	0.18*,†	0.06–0.53†	0.20*,†	0.07–0.60†	0.28†	0.08–0.95†
Total LA emptying fraction (per 5%)	149	0.80*,†	0.70–0.91†	0.72*,†	0.61–0.85†	0.76*,†	0.64–0.90†	0.80†	0.67–0.97†
LV structure									
EF <55%	149	2.03	0.78–5.24	2.09	0.78–5.60	2.51	0.83–7.58	4.45†	1.13–17.56†
LV EF (per 5%)	149	0.76†	0.61–0.94†	0.74†	0.59–0.93†	0.75†	0.58–0.97†	0.66†	0.48–0.90†
LV end-diastolic volume (per 5 mL/m^2)	141	1.12†	1.02–1.24†	1.12†	1.01–1.24†	1.10	0.99–1.24	1.11	0.96–1.29
LV end-systolic volume (per 5 mL/m^2	140	1.18†	1.02–1.37†	1.18†	1.01–1.37†	1.19	0.98–1.43	1.24	0.97–1.59
LV end-diastolic internal diameter, cm	149	2.56*,†	1.43–4.60†	2.51*,†	1.36–4.61†	1.91	0.97–3.76	2.70†	1.17–6.20†
Diastolic function									
Mitral E/A ratio	140	2.90*,†	1.75–4.81†	3.45*,†	2.00–5.94†	3.17*,†	1.82–5.53†	2.25*,†	1.25–4.06†
E prime average, cm/s	133	1.11	0.93–1.32	1.07	0.89–1.29	1.05	0.86–1.28	1.01	0.78–1.30
Mitral E/E prime ratio	131	1.03	0.97–1.11	1.06	0.98–1.14	1.05	0.97–1.14	1.10	0.99–1.23

Adjustment models: Model 1: Age (years), sex, Black race; Model 2: Model 1+BMI (kg/m^2), LDL (mg/dL), HgA1C (%), systolic blood pressure (mm Hg), current smoker, Model 3: Model 2+AF. Gray shading: Increase (more positive) in late negative peak strain rate and early negative peak strain rate is typically thought of as poorer or worse strain function, higher values indicate better functioning for other variables. AF indicates atrial fibrillation; BMI, body mass index; EF, ejection fraction; HgA1C, hemoglobin A1C; LA, left atrial; LASre, early left atrial strain rate; LDL, low-density lipoprotein; LV, left ventricular; and OR, odds ratio.

*Indicates associations that retain significance after adjusting for multiple comparisons (Bonferroni correction).

†Statistical significance under the 2-sided $P<0.05$ assumption.

Table 3. Multivariable Logistic Regression of Cardiac Variables With Cardioembolic Stroke Subtype Among Those Without a History of Atrial Fibrillation

Cardiac Variable	Number of Observations With Available Data	Univariate	95% CI	Model 1 OR	95% CI	Model 2 OR	95% CI
LA volumes							
LA anteroposterior maximum systolic diameter, cm	118	2.84*	1.13–7.15*	6.09*	1.89–19.58*	7.34*	1.41–38.31*
Maximum LA volume (LAVmax, mL/m^2)	116	1.03*	0.99–1.07*	1.05*	1.001–1.09*	1.04	0.99–1.10
Minimum LA volume (LAVmin, mL/m^2)	116	1.03	0.99–1.08	1.07*	1.01–1.12*	1.04	0.98–1.10
Pre-atrial contraction LA volume (LAVpreA, mL/m^2)	108	1.01	0.96–1.05	1.03	0.98–1.08	1.01	0.95–1.07
LA active phase							
Late negative peak strain rate (LASra, s^{-1})	104	1.52	0.79–2.96	1.45	0.72–2.94	1.16	0.51–2.68
Active LA emptying fraction (per 5%)	110	0.57*	0.40–0.82*	0.52*	0.34–0.80*	0.51*	0.30–0.88*
LA conduit phase							
Early negative peak strain rate (LASre, s^{-1})	107	0.84	0.46–1.51	1.55	0.67–3.63	1.72	0.69–4.29
Passive LA emptying fraction (per 5%)	110	1.12	0.91–1.39	0.96	0.75–1.24	1.01	0.77–1.34
LA reservoir phase							
Maximum global longitudinal strain (LSmax, per 5%)	111	0.89	0.66–1.19	0.75	0.55–1.03	0.74	0.52–1.06
Systolic peak strain rate, s^{-1}	111	0.87	0.26–2.98	0.46	0.11–1.91	0.48	0.10–2.24
Total LA emptying fraction (per 5%)	119	0.83	0.68–1.02	0.72*	0.56–0.92*	0.78	0.59–1.03
LV structure							
EF <55%	118	4.12*	1.13–14.97*	7.00*	1.53–31.96*	27.16*	2.40–306.89*
LV ejection fraction (per 5%)	115	0.65*	0.47–0.90*	0.54*	0.35–0.85*	0.39*	0.18–0.84*
LV end-diastolic volume (per 5 mL/m^2)	113	1.18*	1.02–1.35*	1.21*	1.02–1.43*	1.18	0.98–1.43
LV end-systolic volume (per 5 mL/m^2)	112	1.27*	1.03–1.57*	1.34*	1.02–1.77*	1.38	0.98–1.95
LV end-diastolic internal diameter, cm	118	5.14*	2.00–13.20*	8.25*	2.46–27.66*	8.32*	1.93–35.79*
Diastolic function							
Mitral E/A ratio	111	3.37	1.13–10.06	3.12	0.85–11.51	4.94	0.78–31.20
E prime average, cm/s	104	1.15	0.89–1.49	0.94	0.68–1.30	0.81	0.54–1.23
Mitral E/E prime ratio	103	1.02	0.92–1.13	1.07	0.95–1.21	1.16	0.97–1.38

Adjustment models: Model 1: age (years), sex, Black race; Model 2: Model 1+BMI (kg/m^2), LDL (mg/dL), HgA1C (%), systolic blood pressure (mm Hg), current smoker. Gray shading: Increase (more positive) in late negative peak strain rate and early negative peak strain rate is typically thought of as poorer or worse strain function, higher values indicate better functioning for other variables. BMI indicates body mass index; EF, ejection fraction; HgA1C, hemoglobin A1C; LA, left atrial; LASra, late left atrial strain rate; LASre, early left atrial strain rate; LAVpreA, pre-atrial contraction left atrial volume; LDL, low-density lipoprotein; LSmax, maximum global longitudinal strain; LV, left ventricular; and OR, odds ratio.

*Statistical significance under the 2-sided $P<0.05$ assumption.

Table 4. Multivariable Logistic Regression of Cardiac Variables With Stroke of Unknown Cause, Versus Other Stroke Subtypes (Excluding Cardioembolic Stroke)

Cardiac Variable	Number of Observations With Available Data	Univariate	95% CI	Model 1 OR	95% CI	Model 2 OR	95% CI	Model 3 OR	95% CI
LA volumes									
LA anteroposterior maximum systolic diameter, cm	122	1.35	0.72–2.54	1.50	0.75–3.02	1.67	0.74–3.78	1.86	0.79–4.41
Maximum LA volume (LAVmax, mL/m^2)	119	1.02*	1.00–1.05*	1.03*	1.003–1.06*	1.03	0.999–1.06	1.03*	1.001–1.06*
Minimum LA volume (LAVmin, mL/m^2)	119	1.03*	1.00–1.06*	1.04*	1.003–1.08*	1.04	0.999–1.08	1.04*	1.001–1.09*
Pre-atrial contraction LA volume (LAVpreA, mL/m^2)	110	1.02	0.996–1.05	1.03*	1.002–1.07*	1.03	0.999–1.06	1.03	0.999–1.06
LA active phase									
Late negative peak strain rate (LASra, s^{-1})	108	1.27	0.91–1.76	1.34	0.94–1.91	1.28	0.89–1.85	1.28	0.88–1.86
Active LA emptying fraction (per 5%)	113	0.86*	0.74–0.99*	0.85*	0.73–0.99*	0.83*	0.69–0.99*	0.82*	0.68–0.98*
LA conduit phase									
Early negative peak strain rate (LASre, s^{-1})	112	0.85	0.57–1.26	0.82	0.52–1.31	0.77	0.45–1.31	0.77	0.46–1.32
Passive LA emptying fraction (per 5%)	113	1.02	0.88–1.18	1.01	0.86–1.19	1.02	0.86–1.22	1.02	0.86–1.22
LA reservoir phase									
Maximum global longitudinal strain (LSmax, per 5%)	115	0.96	0.80–1.14	0.94	0.78–1.13	0.90	0.73–1.11	0.89	0.72–1.10
Systolic peak strain rate, s^{-1}	115	0.99	0.47–2.08	0.96	0.44–2.07	0.93	0.39–2.19	0.92	0.39–2.19
Total LA emptying fraction (per 5%)	123	0.93	0.82–1.06	0.92	0.80–1.05	0.92	0.79–1.07	0.91	0.78–1.06
LV structure									
EF <55%	122	0.71	0.24–2.10	0.69	0.23–2.09	0.74	0.22–2.47	0.73	0.22–2.45
LV ejection fraction (per 5%)	119	1.17	0.88–1.54	1.18	0.89–1.56	1.17	0.87–1.59	1.17	0.86–1.58
LV end-diastolic volume (per 5 mL/m^2)	116	1.01	0.89–1.13	1.00	0.88–1.13	0.98	0.86–1.12	0.98	0.86–1.12
LV end-systolic volume (per 5 mL/m^2)	115	1.00	0.81–1.24	0.99	0.80–1.23	0.98	0.86–1.12	0.98	0.78–1.24
LV end-diastolic internal diameter, cm	122	1.50	0.84–2.68	1.49	0.82–2.73	1.53	0.78–3.00	1.52	0.77–2.99
Diastolic function									
Mitral E/A ratio	116	1.09	0.61–1.95	1.09	0.60–1.97	1.11	0.59–2.09	1.22	0.62–2.43
E prime average, cm/s	109	0.95	0.79–1.13	0.94	0.79–1.13	0.91	0.74–1.12	0.90	0.73–1.12
Mitral E/E prime ratio	107	1.05	0.98–1.12	1.06	0.99–1.14	1.07	0.99–1.17	1.08	0.99–1.18

Adjustment models: Model 1: age (years), sex, Black race; Model 2: Model 1+BMI (kg/m^2), LDL (mg/dL), HgA1C (%), systolic blood pressure (mm Hg), current smoker; Model 3: Model 2+AF. Gray shading: Increase (more positive) in late negative peak strain rate and early negative peak strain rate is typically thought of as poorer or worse strain function, higher values indicate better functioning for other variables. AF indicates atrial fibrillation; BMI, body mass index; EF, ejection fraction; HgA1C, hemoglobin A1C; LA, left atrial; LASra, late left atrial strain rate; LASre, early left atrial strain rate; LAVmax, left atrial maximum volume; LAVpreA, pre-atrial contraction left atrial volume; LDL, low-density lipoprotein; LSmax, maximum global longitudinal strain; LV, left ventricular; and OR, odds ratio.

*Statistical significance under the 2-sided $P<0.05$ assumption.

Associations that retain significance after adjusting for multiple comparisons (Bonferroni correction), none shown.

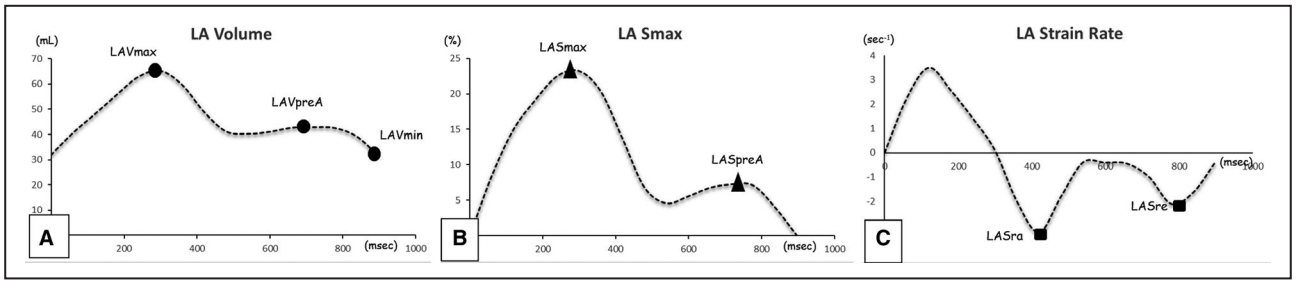

Figure. Two-dimensional speckle tracking volume analysis (A), strain analysis (B), and strain rate analysis (C).
A, Left trial maximal volume (LAVmax, mL/m^2): LAVmax at end systole (just before the mitral valve opens), pre-atrial contraction left atrial (LA) volume (LAVpreA, mL/m^2): LA pre-atrial contraction volume at the onset of the P wave on ECG, minimum volume (LAVmin, mL/m^2): LAVmin at the end diastole (just after the mitral valve closes). Volumes were indexed by body surface area. **B**, Maximum LA global longitudinal strain (LASmax, %); pre-atrial contraction longitudinal strain (LASpreA [%]). **C**, Early LA strain rate (LASre, s^{-1}): First negative strain rate peak at early diastole, late LA strain rate (LASra, s^{-1}): Second negative strain rate peak at late diastole, after the onset of the P wave on ECG.

with a higher active LA emptying fraction had a decreased odds of cryptogenic stroke compared with other stroke subtypes (OR, 0.82, 95% CI, 0.68–0.98). There were no other significant associations with other STE variables or markers of LV structure or diastolic function.

DISCUSSION

In this study, we have demonstrated a significant association between larger LA volumes and several LA strain variables with cardioembolic stroke, specifically confirming our hypothesis that worse LA function would be associated with cardioembolic stroke compared with all other stroke subtypes. We have confirmed the known importance of LA maximum systolic diameter, and its association with cardioembolic stroke, even after several sensitivity analyses,[3,10] and also demonstrated the information that can be garnered from STE, even when applied to clinically obtained TTE.

The form of best cardiac imaging, if any, in patients with stroke has been controversial. Recent guidelines that suggested no role for echocardiography in patients with stroke were redacted,[4,11] with new guidelines stating that echocardiography is "reasonable" in patients with ischemic stroke.[12] With no consensus regarding the standard way to evaluate the cardiovascular function of patients with acute ischemic stroke, it unsurprisingly follows that TTE findings have not been incorporated into clinical decision-making. Transesophageal echocardiography has been suggested to be helpful in patients with cryptogenic stroke,[13] and identification of a patent foramen ovale,[14] which could necessitate closure, but again, no clear guidelines exist.

Our study uniquely considered LA STE strain analysis, a noninvasive method by which to garner information about the phasic function of the LA. The LA functions as an important modulator of LV filling. It is a *reservoir* for pulmonary venous return during ventricular systole, then as a *conduit* for venous return during early diastole, and finally as an *active* pump that augments blood filling during late ventricular diastole.

In our study, we have shown that participants with better LA reservoir function have lower risk for cardioembolic stroke, independent of demographics, risk factors, and AF. Increased LA reservoir function plays an important role in accelerating LV filling by helping to maintain the pressure gradient needed for LV filling in diastole.[15] It follows that more favorable LA reservoir function would be associated with lower odds of cardioembolic stroke, and because the LA and LV are so integrally associated with each other, poorer reservoir function also reflects diastolic dysfunction. It has been suggested that measures of LA reservoir may therefore be a more advanced method by which to truly capture LA dysfunction, rather than LA enlargement alone.

The LA active phase is the most widely recognized phase in the LA cycle when considering potential sources of emboli.[16,17] This was reflected in our findings with an increase in late left atrial strain rate associated with higher odds of cardioembolic stroke and an improvement in active LA emptying fraction with a lower odds of cardioembolic stroke, compared with other stroke subtypes. Other work has demonstrated that LA active function identifies cardiovascular risk in the general population, with a 1 SD decrease in LA emptying fraction associated with a 28% higher risk for AF, potentially suggesting that this may pre-date atrial tachyarrthymia.[18,19] We did not find any significant associations with markers of LA conduit function, but this is not surprising because the conduit phase represents the blood passing through the LA and may not be as robust a measure of LA function.

When considering cryptogenic strokes, or strokes of unknown cause, the observed associations were not consistent and the effect estimates relatively small,

and when excluding this group from the control group in the primary analysis with cardioembolic stroke, the effect estimates between STE markers and cardioembolic stroke were strengthened. This supports our belief that cryptogenic stroke represents a diverse group, and lumping these strokes together into 1 category is likely inadequate to define associations with STE, because the underlying mechanisms of these currently labeled cryptogenic strokes are not homogeneous. When comparing baseline characteristics in our cohort, we found that patients in this group had lower mean LDL than stroke of other subtypes. While we did not formally evaluate patients for embolic stroke of unknown source, it may be that some of our patients with cryptogenic stroke represent an embolic stroke of unknown source mechanism, and therefore have a lower prevalence of traditional stroke risk factors, such as a lower LDL.[20] It may be that these patients have underlying cardiac dysfunction that has not yet been defined,[2,3] or have multiple mechanisms leading to emboli formation. It follows that LA strain coupled with more advanced imaging techniques, or a combination of biomarkers, could help in the future to improve separation of patients who may have an underlying cardiac cause versus other possible mechanisms.

P-wave terminal velocity[21-23] and pro-brain natriuretic peptide[24,25] have been useful in identifying this "diseased" atrial state with an important ongoing clinical trial, ARCADIA (Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke), randomizing patients to different treatments based on the presence of 1 of several LA biomarkers.[26] We suggest that STE might in the future identify patients, such as those being defined in ARCADIA, who have a cardiac source for embolism.

There are limitations to our study. Our patients had a clinical indication for TTE. TTE is standard practice in nearly all patients with stroke admitted to our institution, with the exception of transferred patients from an outside institution who have already obtained a TTE. While this represents routine care, we acknowledge that this may result in selection bias. Not all participants had atrial-specific images and the quality of the TTEs varied, but we used the same TTE vendor for all studies and the analysis was standardized. Additionally, the ascertainment of AF was not uniform and was dependent on the degree of investigation pursued by the clinical team. It is possible cases of AF were underdiagnosed and this could lead to an association falsely driven by undiagnosed AF. As this occurs in standard clinical practice (AF may be underdiagnosed), finding evidence of an association with STE would still be meaningful. It could be speculated that some of our findings are significant simply as a result of multiple comparisons. Our cardiac variables were run in separate models, and the variables chosen reflect different aspects of cardiac function. In consideration of this possibility, we provide results adjusted for multiple comparisons. Finally, we acknowledge that, given the observational nature of the study, there is residual confounding, which might explain some of the observed associations.

In conclusion, we suggest that clinically obtained TTE may be useful in future diagnosis of the cause of strokes, and additionally have shown the potential added value of LA functional analysis that can be obtained from STE. Given that cryptogenic stroke may represent underlying cardiac dysfunction that is not recognized because of incomplete diagnostic strategies or a yet undiscovered cause, LA functional assessment may represent the best next step to a greater understanding of the role of the LA in ischemic stroke. We anticipate a time when a precision-medicine approach, incorporating knowledge about patient cardiac structure, might be used to offer insight into risk of stroke recurrence, risk of AF, and even secondary prevention medication choices.

ARTICLE INFORMATION

Received July 30, 2020; accepted December 1, 2020.

Affiliations

From the Department of Neurology (M.C.J., R.F.G.) and Department of Cardiology (H.D.d., J.A.L.), The Johns Hopkins University School of Medicine, Baltimore, MD; and Department of Cardiology, The University of Pennsylvania Perelman School of Medicine, Philadelphia, PA (S.N.).

Sources of Funding

Dr Johansen received funding for this work from the American Heart Association (#16MCPRP30350000) and the Institute for Clinical and Translational Science (#KL2TR001077-05).

Disclosures

Dr Nazarian reports consulting for CardioSolv and Circle Software and has received honoraria for lectures from Circle Software; Principal investigator for research funding from Biosense Webster, ImriCor, and Siemens, and National Institutes of Health. Dr Gottesman is a former Associate editor for *Neurology*. The remaining authors have no disclosures to report.

Supplementary Material

Data S1
Table S1

REFERENCES

1. Goldberger JJ, Arora R, Green D, Greenland P, Lee DC, Lloyd-Jones DM, Markl M, Ng J, Shah SJ. Evaluating the atrial myopathy underlying atrial fibrillation: identifying the arrhythmogenic and thrombogenic substrate. *Circulation*. 2015;132:278–291. DOI: 10.1161/CIRCULATIONAHA.115.016795.
2. Kamel H, Okin PM, Elkind MS, Iadecola C. Atrial fibrillation and mechanisms of stroke: time for a new model. *Stroke*. 2016;47:895–900. DOI: 10.1161/STROKEAHA.115.012004.
3. Kamel H, Okin PM, Longstreth WT Jr, Elkind MS, Soliman EZ. Atrial cardiopathy: a broadened concept of left atrial thromboembolism beyond atrial fibrillation. *Future Cardiol*. 2015;11:323–331. 10.2217/fca.15.22.
4. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, et al.; American Heart Association Stroke Council. 2018 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*. 2018;49:e46–e110.
5. Mor-Avi V, Lang RM, Badano LP, Belohlavek M, Cardim NM, Derumeaux G, Galderisi M, Marwick T, Nagueh SF, Sengupta PP, et al. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. *Eur J Echocardiogr*. 2011;12:167–205. 10.1093/ejechocard/jer021.
6. Leong DP, Penhall A, Perry R, Shirazi M, Altman M, Chong D, Bradley J, Joseph MX, Selvanayagam JB. Speckle-tracking strain of the left atrium: a transoesophageal echocardiographic validation study. *Eur Heart J Cardiovasc Imaging*. 2013;14:898–905. 10.1093/ehjci/jes323.
7. Mitchell C, Rahko PS, Blauwet LA, Canaday B, Finstuen JA, Foster MC, Horton K, Ogunyankin KO, Palma RA, Velazquez EJ. Guidelines for performing a comprehensive transthoracic echocardiographic examination in adults: recommendations from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2019;32:1–64. 10.1016/j.echo.2018.06.004.
8. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE III. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993;24:35–41. DOI: 10.1161/01.STR.24.1.35.
9. StataCorp. Stata statistical software: release 14. 2015.
10. Gagne Brosseau MS, Boulanger JM, Leblanc N, Berger L, Benzazon M. Left atrium dilatation and multiple vascular territory strokes. *Can J Neurol Sci*. 2014;41:704–708. 10.1017/cjn.2014.40.
11. McCoy CE, Langdorf MI, Lotfipour S. American Heart Association/American Stroke Association deletes sections from 2018 stroke guidelines. *West J Emerg Med*. 2018;19:947–951. 10.5811/westjem.2018.9.39659.
12. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2019;50:e344–e418. DOI: 10.1161/STR.0000000000000211.
13. Katsanos AH, Bhole R, Frogoudaki A, Giannopoulos S, Goyal N, Vrettou A-R, Ikonomidis I, Paraskevaidis I, Pappas K, Parissis J, et al. The value of transesophageal echocardiography for embolic strokes of undetermined source. *Neurology*. 2016;87:988–995. 10.1212/WNL.0000000000003063.
14. Larrue V, Berhoune N, Massabuau P, Calviere L, Raposo N, Viguier A, Nasr N. Etiologic investigation of ischemic stroke in young adults. *Neurology*. 2011;76:1983–1988. 10.1212/WNL.0b013e31821e5517.
15. Morris DA, Takeuchi M, Krisper M, Kohncke C, Bekfani T, Carstensen T, Hassfeld S, Dorenkamp M, Otani K, Takigiku K, et al. Normal values and clinical relevance of left atrial myocardial function analysed by speckle-tracking echocardiography: multicentre study. *Eur Heart J Cardiovasc Imaging*. 2015;16:364–372. 10.1093/ehjci/jeu219.
16. Lima JAC, Ambale-Venkatesh B. Left atrial strain to address the cryptogenic puzzle. *JACC Cardiovasc Imaging*. 2018;11:1566–1568. 10.1016/j.jcmg.2017.08.020.
17. Hoit BD. Left atrial size and function: role in prognosis. *J Am Coll Cardiol*. 2014;63:493–505. 10.1016/j.jacc.2013.10.055.
18. Chinali M, de Simone G, Roman MJ, Bella JN, Liu JE, Lee ET, Best LG, Howard BV, Devereux RB. Left atrial systolic force and cardiovascular outcome. The Strong Heart Study. *Am J Hypertens*. 2005;18:1570–1576; discussion 1577.
19. Vasan RS, Larson MG, Levy D, Galderisi M, Wolf PA, Benjamin EJ; National Heart, Lung, and Blood Institute, National Institutes of Health. Doppler transmitral flow indexes and risk of atrial fibrillation (the Framingham Heart Study). *Am J Cardiol*. 2003;91:1079–1083. 10.1016/S0002-9149(03)00152-8.
20. Li L, Yiin GS, Geraghty OC, Schulz UG, Kuker W, Mehta Z, Rothwell PM; Oxford Vascular Study. Incidence, outcome, risk factors, and long-term prognosis of cryptogenic transient ischaemic attack and ischaemic stroke: a population-based study. *Lancet Neurol*. 2015;14:903–913. 10.1016/S1474-4422(15)00132-5.
21. He J, Tse G, Korantzopoulos P, Letsas KP, Ali-Hasan-Al-Saegh S, Kamel H, Li G, Lip GYH, Liu T. P-wave indices and risk of ischemic stroke: a systematic review and meta-analysis. *Stroke*. 2017;48:2066–2072. DOI: 10.1161/STROKEAHA.117.017293.
22. Kamel H, Soliman EZ, Heckbert SR, Kronmal RA, Longstreth WT Jr, Nazarian S, Okin PM. P-wave morphology and the risk of incident ischemic stroke in the Multi-Ethnic Study of Atherosclerosis. *Stroke*. 2014;45:2786–2788. DOI: 10.1161/STROKEAHA.114.006364.
23. Pirinen J, Putaala J, Aro AL, Surakka I, Haapaniemi A, Kaste M, Haapaniemi E, Tatlisumak T, Lehto M. Resting 12-lead electrocardiogram reveals high-risk sources of cardioembolism in young adult ischemic stroke. *Int J Cardiol*. 2015;198:196–200. 10.1016/j.ijcard.2015.06.095.
24. Llombart V, Antolin-Fontes A, Bustamante A, Giralt D, Rost NS, Furie K, Shibazaki K, Biteker M, Castillo J, Rodríguez-Yáñez M, et al. B-type natriuretic peptides help in cardioembolic stroke diagnosis: pooled data meta-analysis. *Stroke*. 2015;46:1187–1195. DOI: 10.1161/STROKEAHA.114.008311.
25. Rodriguez-Yanez M, Sobrino T, Blanco M, de la Ossa NP, Brea D, Rodriguez-Gonzalez R, Leira R, Davalos A, Castillo J. High serum levels of pro-brain natriuretic peptide (pro BNP) identify cardioembolic origin in undetermined stroke. *Dis Markers*. 2009;26:189–195. DOI: 10.1155/2009/351591.
26. Kamel H, Longstreth WT Jr, Tirschwell DL, Kronmal RA, Broderick JP, Palesch YY, Meinzer C, Dillon C, Ewing I, Spilker JA, et al. The AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke randomized trial: rationale and methods. *Int J Stroke*. 2019;14:207–214. DOI: 10.1177/1747493018799981.

SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

2D end-diastolic volume, end-systolic volume, and left ventricle ejection fraction (LVEF) were measured by biplane disc method (modified Simpson's rule) in the four and two chamber views. Pulse wave Doppler echocardiography was employed to measure the transmitral flow peak velocities from the early (E) and late (A) diastolic phase. Tissue Doppler imaging was applied to calculate the early septal and lateral mitral annulus diastolic peak (E prime). The images were analyzed offline by trained and certified readers, masked to clinical details, using standardized protocols following ASE guidelines. For STE analysis, the LA endocardial surface was manually traced at the end systolic ventricular phase just before the mitral valve open in a counterclockwise direction, from the medial to the lateral mitral annulus, excluding the LA appendage and the ostium of the pulmonary veins. The software automatically propagated these borders across the cardiac cycle. The quality of the generated tracking was verified, with manual adjustments made when necessary. The LA STE inter- and intra-reader reproducibility was made by one expert reader, making the assessments in a random subset of 20 participants. Re-readings were performed 30 days after the initial measurement, blinded to the original analysis.

The three emptying fractions were calculated as follows: Total emptying fraction [(LAVmax – LAVmin)/LAVmax]*100, passive emptying fraction [(LAVmax – LAVpreA)/LAVmax]*100, and active emptying fraction [(LAVpreA – LAVmin)/LAVpreA]*100.

Table S1. Multivariable logistic regression of cardiac variables with cardioembolic stroke subtype versus other, with cryptogenic excluded.

Cardiac variable	Number of observations with available data	Model 1 OR	95% CI	Model 2 OR	95% CI	Model 3 OR	95% CI
LA Volumes							
LA antero-posterior maximum systolic diameter (cm)	113	**5.73**	**2.44-13.48**	**5.90**	**2.13-16.34**	**5.29**	**1.55-18.11**
Maximum LA volume (LAVmax, ml/m2)	112	**1.05**	**1.02-1.09**	**1.06**	**1.02-1.10**	1.04	0.99-1.08
Minimum LA volume (LAVmin, ml/m2)	112	**1.10**	**1.05-1.16**	**1.10**	**1.05-1.16**	**1.07**	**1.01-1.14**
Pre-atrial contraction LA volume (LAVpre, ml/m2)	96	**1.04**	**1.001-1.08**	1.04	0.99-1.08	1.03	0.98-1.08
LA active phase							
Late negative peak strain rate (LASra, sec^{-1})	97	**2.32**	**1.38-3.90**	**2.14**	**1.23-3.71**	1.83	0.94-3.53
Active LA emptying fraction (per 5%)	98	**0.66**	**0.52-0.84**	**0.70**	**0.55-0.89**	**0.72**	**0.55-0.93**
LA conduit phase							
Early negative peak strain rate (LASre, sec^{-1})	101	1.31	0.74-2.31	1.28	0.69-2.37	1.57	0.65-3.77
Passive LA emptying fraction (per 5%)	98	0.98	0.81-1.20	1.00	0.80-1.24	0.96	0.74-1.23
LA reservoir phase							
Maximum global longitudinal strain (LSmax, per 5%)	106	**0.61**	**0.47-0.78**	**0.63**	**0.49-0.82**	**0.67**	**0.50-0.90**

Systolic peak strain rate (sec^{-1})	106	**0.14**	**0.04-0.45**	**0.17**	**0.05-0.57**	**0.24**	**0.06-0.93**
Total LA emptying fraction (per 5%)	114	**0.68**	**0.57-0.82**	**0.71**	**0.58-0.87**	**0.74**	**0.59-0.93**
LV Structure							
EF<55%	113	1.97	0.69-5.59	2.42	0.71-8.23	4.48	0.95-21.04
LV ejection fraction (per 5%)	109	**0.76**	**0.60-0.97**	0.78	0.59-1.04	**0.69**	**0.49-0.96**
LV end-diastolic volume (per 5ml/m2)	107	**1.11**	**1.01-1.23**	1.09	0.96-1.23	1.10	0.94-1.29
LV end-systolic volume (per 5ml/m2)	107	1.17	0.99-1.38	1.16	0.94-1.43	1.21	0.93-1.58
LV end-diastolic internal diameter (cm)	113	**2.77**	**1.43-5.39**	2.17	0.94-1.43	**2.83**	**1.13-7.08**
Diastolic Function							
Mitral E/A ratio	99	1.09	0.89-1.33	**3.14**	**1.70-5.77**	**2.38**	**1.21-4.65**
E prime average (cm/sec)	100	1.06	0.87-1.29	0.99	0.79-1.23	0.92	0.69-1.24
Mitral E/E prime ratio	99	1.10	0.99-1.21	**1.12**	**1.01-1.24**	1.13	0.99-1.29

LV=Left ventricular, LA=Left atrial, CI=Confidence Interval, BMI=Body mass index, HgA1C=Hemoglobin A1C, AF=Atrial Fibrillation.

Adjustment models: Model 1: Age(years), sex, black race; Model 2: Model 1+BMI(kg/m^2), LDL(mg/dL), HgA1C(%), systolic blood pressure (mmHg), current smoker; Model3: Model2+AF

Bolded numbers: Statistical significance under the two-sided $p<0.05$ assumption

Gray shading: Increase (more positive) in late negative peak strain rate and early negative peak strain rate is typically thought of as poorer or worse strain function, higher values indicate better functioning for other variables.