Left Atrial Mechanical Function and Incident Ischemic Cerebrovascular Events Independent of AF:

Insights From the MESA Study

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Abstract

OBJECTIVES—This study sought to assess the association of baseline left atrial (LA) phasic function measured with cardia magnetic resonance (CMR) and incident ischemic cerebrovascular events (CVE).

BACKGROUND—LA remodeling is a known predictor of atrial fibrillation (AF), which is a risk factor for ischemic CVE. Despite studies showing an association between LA remodeling and ischemic CVE, the association of LA mechanical function with ischemic CVE in a population free of known cardiovascular disease is not fully studied.

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METHODS—Phasic LA volumes; total, passive, and active LA emptying fractions (LAEF); and peak longitudinal LA strain were measured using feature-tracking CMR in 4,261 MESA (Multi-Ethnic Study of Atherosclerosis) participants (61 ± 10 years of age; 4 8 % male). All individuals were free of clinical cardiovascular disease at baseline. Participants were followed for 11.6 ± 3.5 years for the diagnosis of incident ischemic CVE, defined as ischemic stroke or transient ischemic attack adjudicated by vascular neurologists.

RESULTS—During the follow-up, 193 (1.26 per 1,000 person-years) ischemic CVE (134 ischemic strokes and 59 TIAs) occurred. Individuals with incident ischemic CVE had larger LA volumes and lower passive, active, and total LAEFs at baseline. In multivariate analysis adjusted for known CVE risk factors, left ventricular mass and interim AF, total LAEF was associated with incident ischemic CVE (hazard ratio [HR]: 0.85 per SD; 9 5 % confidence interval [Cl]: 0.74 to 0.98; p = 0.027). The unadjusted HR for the lowest tertile of total LAEF compared to the highest tertile was 2.0 (95% Cl: 1.43 to 2.79; p < 0.001), and the adjusted HR was 1.47 (95% Cl: 1.04 to 2.05; p = 0.031). Addition of total LAEF to known clinical risk factors of CVE and left ventricular mass resulted in an improved predictive accuracy (C statistic of 0.76 vs. 0.73, respectively; p = 0.039).

CONCLUSIONS—Reduced total LAEF was associated with incident ischemic CVE independent of known cerebrovascular risk factors and incident AF. Assessment of LA function may add further information in stratifying asymptomatic individuals at risk for ischemic stroke.

Graphical Abstract
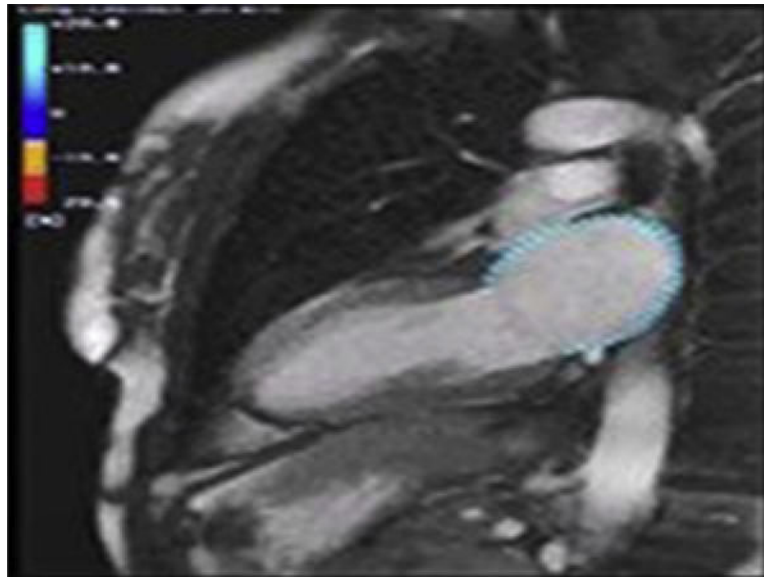
Keywords

atrial fibrillation; atrial function; cardiac magnetic resonance; ischemic stroke; left atrial remodeling

Left atrial (LA) remodeling consists of mechanical, electrical, and structural changes. These changes are present before atrial fibrillation (AF) development and worsen with

development of AF (1–3). In AF patients, the greater extent of LA remodeling is associated with worse outcomes, especially with a higher prevalence of cerebrovascular events (CVE) (4,5). Nonetheless, emerging data suggest an association between atrial structural changes such as increased LA size (6,7), electrical abnormalities of the P-wave on surface electrocardiography (ECG) (8–11), and elevated levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) (11) with risk of ischemic CVE independent of AF. The common hypothesis connecting LA remodeling and ischemic CVE is posited to be the potential role of LA mechanical dysfunction in blood stasis and therefore thromboembolism. Despite several prospective studies investigating the association of LA remodeling and ischemic stroke (Supplemental Table 1), no study has investigated the association of LA mechanical function with ischemic CVE in a population free of clinical cardiovascular disease. Accordingly, this study sought to examine the association of baseline LA mechanical function measured with CMR, the gold standard modality for assessing myocardial function, and incident ischemic CVE in a multiethnic population free of clinical cardiovascular disease at baseline. The hypothesis was that worse baseline LA function would be associated with a higher incidence of ischemic CVE independent of interim AF.

METHODS

STUDY POPULATION.

This study is embedded in the MESA (Multi-Ethnic Study of Atherosclerosis) study. Briefly, between July 2000 and August 2002, MESA recruited 6,814 individuals from 6 U.S. communities in North Carolina, New York, Maryland, Illinois, Minnesota, and California (12). Of the 6,814 participants, 5,098 underwent cardiac magnetic resonance (CMR) imaging (75%) and 5,004 (73%) had technically adequate data. The participants were between 45 and 84 years of age and were from 4 different self-reported racial/ethnic backgrounds (white, African-American, Hispanic, and Chinese). All participants were free of any clinically apparent cardiovascular disease at baseline. The Institutional Review Boards of the participating sites approved the study, and all participants gave written informed consent. The description and methods of collecting covariates have been explained in the Supplemental Appendix.

FOLLOW-UP.

In addition to 5 follow-up examinations, a telephone interviewer contacted each participant approximately every 9 months to inquire about hospital admissions, cardiovascular outpatient diagnoses, and deaths. Medical records were successfully obtained for 98% of reported hospitalized cardiovascular events and 95% of reported outpatient cardiovascular diagnostic encounters.

ADJUDICATION OF EVENTS.

A committee that included neurologists, cardiologists, and physician epidemiologists adjudicated strokes, transient ischemic attacks (TIA), and other cardiovascular events (12). Ischemic stroke consisted of rapid onset of a documented focal neurologic deficit lasting 24 h or until death or, if <24 h, there was a clinically relevant infarction shown on brain imaging. Patients with focal neurologic deficits secondary to hemorrhagic stroke, brain

trauma, tumor, infection, or other nonvascular cause were excluded. TIA consisted of 1 or more documented episodes of focal neurologic deficit lasting 30 s to 24 h and without brain imaging suggesting stroke. For the purposes of this study, ischemic CVE was defined as fatal or nonfatal ischemic stroke or TIA.

Incident AF during follow-up was identified by using a combination of hospitalization surveillance, follow-up ECG in 2010 to 2012, and, for participants enrolled in fee-for-service Medicare, from inpatient, outpatient, and physician claims. The International Classification of Diseases-9th Revision, diagnostic code 427.31 (atrial fibrillation) or 427.31 (atrial flutter) in any position was considered evidence of AF. If the first AF claim occurred before the baseline MESA examination, the participant was considered to have prevalent AF and was excluded from the analysis.

IMAGE ANALYSIS.

Baseline MR images were acquired using 1.5-T CMR scanners, either Signa LX or CVi (GE Medical Systems, Waukesha, Wisconsin) or Symphony or Sonata (Siemens Medical Systems, Erlangen, Germany). Long-axis cine images were obtained from 2- and 4-chamber views, using ECG-gated fast gradient-echo pulse sequence. All cine images were acquired with a temporal resolution of approximately 50 ms. A stack of short-axis images recorded at end diastole was obtained for the LV mass assessment (13).

Five experienced operators analyzed all images in a core laboratory at Johns Hopkins University. Multimodal tissue tracking software (MTT, version 5.0, Toshiba, Japan) was used to quantify LA strain and phasic volumes from baseline 4- and 2-chamber cine CMR images. This method has been previously validated with excellent reproducibility (intraclass correlation coefficients between 0.90 to 0.97 for LA volumes and strain) (14). Endocardial and epicardial LA borders were defined at end-systole. In the 4-chamber view, the LA border started from the medial side of the mitral annulus and included interatrial septum, posterior, and lateral LA walls and ended at the lateral mitral annulus. In the 2-chamber view, the analyzed atrial border started from anterior mitral annulus and continued over the LA roof, the posterior wall, and the floor of the LA and ended at the inferior mitral annulus. Using the defined borders, the software then tracked the LA myocardium in subsequent frames (Video 1). The operator then followed the generated contours during the cardiac cycle for quality control. Images with poor tracking and/or foreshortened images were excluded. In each frame, the LA volume was calculated using this previously validated formula: [volume = $(0.848 \ \text{area}_{4ch} \times \text{area}_{2ch})/([\text{length}_{2ch} + \text{length}_{4ch}]/2)$ (15). Maximum, minimum, and pre-atrial contraction LA volumes were extracted from volume curves which were calculated from apical 4- and 2-chamber views. The point on the LA volume curve during diastole just before the fast descent following a period of stability in LA volume was defined as pre-atrial (PreA) contraction volume. At that point, the atrial strain rate is equal to zero. If such a point could not be identified from the volume curve, only maximum and minimum volumes were reported. All measured volumes were indexed to body surface area. An example of an LA volume curve during a cardiac cycle is shown in Figure 1.

We then calculated the volumetric LA function as follows:

Passive LA emptying fraction (LAEF) (in %):

$$100 \cdot [LAV_{max} - LAV_{PreA}]/LAV_{max}$$

Active LA emptying fraction (active LAEF) (in %):

$$100 \cdot [LAV_{PreA} - LAV_{min}]/LAV_{PreA}$$

Total LA emptying fraction (total LAEF in %):

$$100 \cdot [LAV_{max} - LAV_{min}]/LAV_{max}$$

STRAIN MEASUREMENT.

The software calculated the global longitudinal atrial strain by measuring fractional shortening or lengthening of each LA segment in 2- and 4-chamber views, using the defined LA borders during the cardiac cycle and averaging all segments. Global peak longitudinal LA strain (peak LA strain) was then extracted from the global longitudinal strain curve (Figure 1).

STATISTICAL ANALYSIS.

The baseline characteristics and LA parameters were compared between participants with and those without CVE, using the chi-square and *t* tests. Multivariate Cox proportional hazards models were used to determine the association of LA variables with incident ischemic CVE. Covariates were selected on the basis of the conceptual model and the association of these factors with incident ischemic CVE. The potential co-linearity was examined between continuous variables. Variables with Spearman correlation coefficient >0.50 were not included in the same multivariate model. The models included age, sex, race/ethnicity, body mass index, systolic and diastolic blood pressures, total cholesterol, high-density lipoprotein, cigarette smoking status, blood pressure medication use, statin use, diabetes mellitus, and left ventricular mass (model 1). To explore whether AF mediated associations between LA parameters and ischemic CVE, adjustments were also made for interim incident AF as a time-dependent covariate (model 2). Because in many cases the clinical diagnosis of AF follows a long period of subclinical AF (16), AF was adjusted for as a time-fixed covariate (i.e., with the assumption of AF presence since baseline as a subclinical form) (model 3). To explore the dose-response relationship of LA function with ischemic CVE, variables were modeled with restricted quadratic splines with knots at the 5th, 50th, and 95th percentiles of their distribution. To assess the additive value of LA parameters to the known ischemic CVE risk factors in predicting CVE, the area under the curve (AUC) was derived from receiver operating characteristic curve analysis (ROC). To assess the association of LA function and ischemic CVE in the absence of other known risk factors of stroke, the models were rerun in individuals with low stroke risk (CHA_2DS_2-VASc [Congestive heart failure, Hypertension, Age 75 years, Diabetes mellitus, Prior stroke, transient ischemic attack [TIA], or thromboembolism, Vascular disease, Age 65–74 years, Sex category [female] score 1) and in those with no interim incident AF. In an

additional step, adjustment was also made for the P-wave terminal force in lead V_1 (PTFV$_1$) and NT-proBNP as another known marker of LA remodeling to assess additive values of mechanical LA function variables. Statistical analyses were performed using STATA version 12.1 software (STATA Corp., College Station, Texas).

RESULTS

Of 5,004 participants with baseline CMR, 66 were excluded due to AF diagnosis prior to the enrollment. Other participants (n = 677) were excluded due to lack of either 2- or 4-chamber cine images through the LA, poor image quality, or low temporal resolution. It was feasible to measure LA volume in 4,261 participants (86.3%) and LA function in 4,214 participants (85.3%). After a mean follow-up of 11.6 ± 3.5 years, 193 individuals (4.5% of 4,261, 1.26 per 1,000 person-years) experienced incident ischemic CVE (134 cerebral infarctions and 59 TIAs).

Participant characteristics are summarized in Table 1. Individuals with ischemic CVE were older, had a less favorable cardiovascular risk profile, higher LV mass, higher levels of NT-proBNP, and higher prevalence of abnormal PTFVI. Participants with incident ischemic CVEs also developed more AF (30.7% vs. 12.4%, respectively) during the follow-up than those who did not have ischemic CVE. Of 193 participants with incident ischemic CVE, 34 (17.6%) were diagnosed with AF prior to or at the time of ischemic CVE, and 24 (12.4%) were diagnosed with AF after incident ischemic CVE, whereas 135 participants (70.0%) did not develop clinically recognized AF during the follow-up.

Table 2 presents variables of LA volume and function. Participants with incident ischemic CVE had larger LA volumes with lower passive, active, and total LAEFs at baseline than individuals who did not develop ischemic CVE. However, LA longitudinal strain was comparable between the 2 groups. LA variables were also compared by strata of incident AF and incident CVE. As illustrated in Figure 2, individuals with either incident ischemic CVE or AF had larger LA with lower function at baseline than those with neither incident AF nor incident CVE (p < 0.001 for all LA variables).

In the multivariate model (model 1), minimum but not maximum LA volume index was associated with incident ischemic CVE (hazard ratio [HR]: 1.18 per SD of left atrial volume index [LAVI$_{min}$]; 95% confidence interval [CI]: 1.04 to 1.34). Among LA functional variables, active and total LAEF were inversely associated with incident ischemic CVE (HR for active LAEF: 0.84 per SD; 95% Cl: 0.73 to 0.97; HR for total LAEF: 0.80 per SD; 95% CI: 0.69 to 0.92). After AF was adjusted for, whether as a time-dependent or a time-fixed covariate, the association attenuated but remained significant for total LAEF (HR: 0.85 per SD; 95% CI: 0.71 to 0.97 in model 2, and HR: 0.83 per SD; 95% CI: 0.71 to 0.97 in model 3). However, the associations between LAVI$_{min}$ and active LAEF with ischemic CVE were not significant after adjusting for interim AF. These associations are shown in Table 3.

Figure 3 shows the association between total LAEF and ischemic CVE, using a restricted cubic spline model adjusted for baseline covariates. When assessed by tertiles, the relationship between total LAEF and incident ischemic CVE was significant and graded.

When adjusted for covariates, the lowest tertile of total LAEF compared to the highest tertile was 2.0 (95% CI: 1.43 to 2.79; p < 0.001), and adjusted for demographics, the clinical risk factors and interim AF was 1.47 (95% CI: 1.04 to 2.05; p 0.031). Figure 4 shows the Kaplan-Meier analyses graphs for incident ischemic CVE based on tertiles of total LAEF.

To examine the incremental value of total LAEF in risk stratification of participants for ischemic CVE, the AUC was calculated in a basic model including variables in model 1. The addition of total LAEF to the basic model improved the AUC from 0.73 to 0.76 (p = 0.039).

SUBGROUP ANALYSES.

In 3,525 participants with available measurements, additional adjustment for log-transformed NT-proBNP and $PFTV_1$, the association between total LAEF and ischemic CVE remained essentially unchanged (Supplemental Table 2).

To minimize the possibility of residual bias and to assess the value of LA remodeling in participants with low baseline stroke risk, a subanalysis was performed in 2,187 individuals with a CHA_2DS_2-VASc score of 1. In model 1, after adjusting for remaining stroke risk factors not reflected in CHA_2DS_2-VASc score, total LAEF was still significantly associated with ischemic CVE (HR per SD: 0.58; 95% CI: 0.44 to 0.77). The association remained significant after adjusting for interim incident AF in models 2 and 3 as a time-dependent or time-fixed covariate, respectively (HR: 0.60 per SD; 95% CI: 0.45 to 0.80 in model 2, and HR: 0.60 per SD; 95% CI: 0.45 to 0.80 in model 3). Figure 5 shows the Kaplan-Meier analyses graphs for incident ischemic CVE based on tertiles of total LAEF in participants with a CHA_2DS_2-VASc score 1. The association between total LAEF and ischemic CVE also remained significant after excluding individuals with interim incident AF (HR: 0.67 per SD; 95% CI: 0.49 to 0.93).

DISCUSSION

This prospective multiethnic population-based study of individuals free of clinical cardiovascular disease demonstrated an inverse association between total LAEF, as a marker of global/reservoir LA function, and incident ischemic CVE. This association was independent of known cerebrovascular disease risk factors and interim incident AF and persisted in participants with low stroke risk factors. Total LAEF improved risk stratification of individuals with no known cardiovascular disease for ischemic stroke development.

Alterations in LA size and, more importantly, LA function are associated with cardiovascular disease in the general population and with poor outcomes in patients with cardiovascular disease (2). The contribution of LA remodeling is even more prominent in the pathogenesis of AF and stroke. Therefore, in the past few years significant efforts have been directed toward quantification and implementation of LA remodeling measurements in risk stratification of patients with cardiovascular disease, especially those with AF. Changes in P-wave morphology and elevated NT-proBNP concentration as indirect markers of LA structural and mechanical changes were associated with incident CVE independent of AF (8–11,17). These observations suggest that LA mechanical dysfunction may directly affect the stroke risk. Due to the anatomic profile of LA, direct assessment of LA mechanical

function is challenging. In this study feature-tracking CMR was used to analyze phasic LA function by using a volumetric method to calculate LAEFs and deformation analysis to measure LA strain during the cardiac cycle.

LEFT ATRIAL SIZE AND FUNCTION IN RELATION TO ISCHEMIC STROKE.

LA enlargement is associated with incidence or prevalence of stroke in a general population and in patients with previous stroke independent of AF (6,7,18). Similar findings are observed in elderly patients (19) and in women (20). In contrast, in our study, minimum LA volume was a risk factor for incident CVE; however, this association was not independent of interim AF.

Most studies of LA mechanical function and stroke have been performed in patients with known cardiac disease, especially AF, or those with previous ischemic stroke (3,21). Those studies found lower LAEF, strain, and strain rates in patients with or without AF but with previous stroke (22–24). Lower LA strain is also associated with high-risk transesophageal echoradiography features of cardioembolism in patients who presented with acute stroke (25). In patients with AF, LA reservoir function has incremental value when added to the CHA_2DS_2-VASc score for risk of previous stroke events (4,5). In a study on 983 individuals with stable coronary heart disease, lower LA functional index was associated with ischemic stroke (26). Other supporting evidence of the role of LA contractile dysfunction in stroke comes from cardiac conditions such as amyloidosis and myosin light chain mutation, which involve predominantly LA and are associated with higher risk of stroke, even in the absence of AF (27,28).

To the best of the present authors' knowledge, no other prospective study has investigated the association between mechanical LA function and ischemic CVE in a general population free of clinical cardiovascular disease. The present study showed an association between lower LA reservoir function and incident ischemic CVE independent of interim AF. Our findings complement previous retrospective and cross-sectional studies in patients with stroke and known AF. Importantly, in the present study this association persisted in low-risk population with a CHA_2DS_2-VASc score of   1 and was additive to other known markers of LA remodeling.

ATRIAL REMODELING AND ISCHEMIC STROKE: POSSIBLE MECHANISMS.

The exact contribution of LA to the pathogenesis of thromboembolic events is not fully understood. Results from population-based studies confirm the presence of LA remodeling before AF development (1,29). Therefore, LA dysfunction might be a marker of future AF episodes that leads to ischemic CVE. However, observations from patients with implanted rhythm monitoring devices do not confirm a temporal association between AF episodes and stroke events. In the ASSERT (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial), only 8% of the patients with stroke had AF episodes within 30 days prior to their CVE, whereas 16% of the stroke cases had their first AF episode after their strokes (30). Another study of patients with dual-chamber and biventricular defibrillators also found no temporal association between atrial tachyarrhythmia and thromboembolism (31). In this study, only 30.7% of participants

with ischemic CVE had interim incident AF. Furthermore, the association between LA remodeling and ischemic CVE was present in those with no incident AF. Electrical markers of atrial myopathy and LA size have been specifically associated with cryptogenic or embolic stroke and not with cerebral small vessel occlusion (9,17,32). Therefore, in addition to be a marker of future AF episodes, LA dysfunction may be an independent risk factor for blood stasis and thromboembolism events. Although this hypothesis is intuitively appealing, several studies suggest a more complex stroke mechanism in patients with AF or atrial myopathy. Many of the underlying processes leading to atrial myopathy such as aging, hypertension, diabetes, smoking, inflammation, heart failure, and LV hypertrophy are also known risk factors for stroke unrelated to emboli from LA (Central Illustration) (2,3). A cross-sectional study shows an association between LA dysfunction and known stroke risk factors and also with silent infarcts found in brain MRI (33). Although there is a strong correlation between AF and ischemic stroke, 10% of patients with lacunar stroke also have AF. Large-artery atherosclerosis is also more common in AF patients compared to those with no AF (34).

In the present study, the association between atrial mechanical dysfunction and incident ischemic CVE was attenuated after adjustments were made for known stroke risk factors. This indicates that LA dysfunction may be a marker for coexisting risk factors leading to stroke through mechanisms outside the LA. Although a higher incidence of ischemic CVE is still found in individuals with lower total LAEF but otherwise low-stroke risk factors (e.g., CHA_2DS_2-VASc score 1), data for ischemic stroke subtypes were not available for this study.

POTENTIAL CLINICAL IMPLICATIONS.

Several studies have shown the usefulness of including mechanical LA functional measures in risk stratification of individuals for ischemic CVE in the absence of clinical AF. However, except for the maximum LA volume, other parameters of LA function are not routinely measured in clinical settings. CMR was used for analyzing LA function, but those measurements were also obtainable using 2D or 3D echocardiography in clinical settings. Diagnosis of atrial cardiomyopathy may also have therapeutic and preventive implications. Emerging evidence supports upstream effects of angiotensin-converting enzyme inhibitors, aldosterone blockers, and statins in prevention of AF in high-risk populations (35–37). Although data for the role of these medications in LA reverse remodeling in humans are limited, future studies of the effects of risk-factor modifications and also medical therapy on LA reverse remodeling and subsequent incident ischemic stroke in susceptible populations are of great value. In addition, presence of atrial myopathy may be useful for decision making in initiation of anticoagulation in a high-risk population. Results of the ongoing ARCADIA (Atrial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke) trial will help us to understand whether diagnosis of atrial cardiomyopathy in ischemic stroke patients with no known AF warrants anticoagulation (38). However, use of a combination of low-dose anticoagulation and aspirin such as that shown to be beneficial in the COMPASS (Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease) trial needs further investigations (39).

STUDY LIMITATIONS.

A few limitations in this study should be addressed. CMR images were acquired in the time period between 2000 and 2002; since that time, cine CMR sequences have improved, with higher temporal and spatial resolution. Therefore, CMR images were not interpretable for the assessment of LA function in 14% of the study population. However, this percentage is about the same or lower than those in other studies using speckle-tracking echocardiography in measurements of LA function (40). The lower temporal resolution might have resulted in lower accuracy of strain measurements. The area-length method was used to measure LA volumes. Therefore, the calculated volumes may be an underestimation of the true volumes by 11.5% to 20%, depending on the alignment of the acquired slice with true orientation of LA (15,41). However, this method is widely used in clinical and research studies (42). Incident AF was identified based on hospital discharge codes and MESA follow-up visits, which may underestimate AF diagnosis as many of AF cases are asymptomatic and do not require hospitalization. A validation substudy of 45 MESA participants with the diagnosis of AF based on hospital discharge codes confirmed the diagnosis of AF in 93% of the hospitalizations (43). Additionally, based on a systematic review using information from 16 unique studies, a large proportion of prevalent AF cases identified by International Classification of Diseases, Ninth Revision codes were valid (positive predictive value 70% to 96%; median, 89%) (44). Individuals with the new diagnosis of AF may have had undiagnosed subclinical AF at baseline. AF was adjusted as both a time-dependent variable and time-fixed covariate with the assumption of AF presence since baseline.

CONCLUSIONS

An inverse association was found between LA reservoir function, measured as total LAEF, and the risk of CVE. This association was independent of known cerebrovascular risk factors and AF. These findings complement other studies in questioning whether AF itself is always required in the pathogenesis of cardiac thromboembolism. These findings suggest possible value of LA functional parameters in stratification of individuals at risk for ischemic CVE especially those with no clear evidence of AF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

ABBREVIATIONS AND ACRONYMS

AF	atrial fibrillation
CMR	cardiac magnetic resonance
CVE	cerebrovascular events
LA	left atrium
LAEF	left atrial emptying fraction
LAV	left atrial volume
LAVI	left atrial volume index
TIA	transient ischemic attack

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:

In individuals with no clinical cardiovascular disease, CMR measured LA mechanical dysfunction is associated with incident ischemic CVE independent of known cardiovascular risk factors and interim AF. This association persisted in individuals with low CVE risk factors. Addition of LA mechanical function to known clinical risk factors of ischemic CVE improves risk prediction accuracy.

TRANSLATIONAL OUTLOOK:

Future studies are required to explore possible benefits of anticoagulation in patients with atrial myopathy in the absence of known AF. In addition, potential role of interventions leading to atrial reverse remodeling in reducing the risk of stroke needs to be investigated.
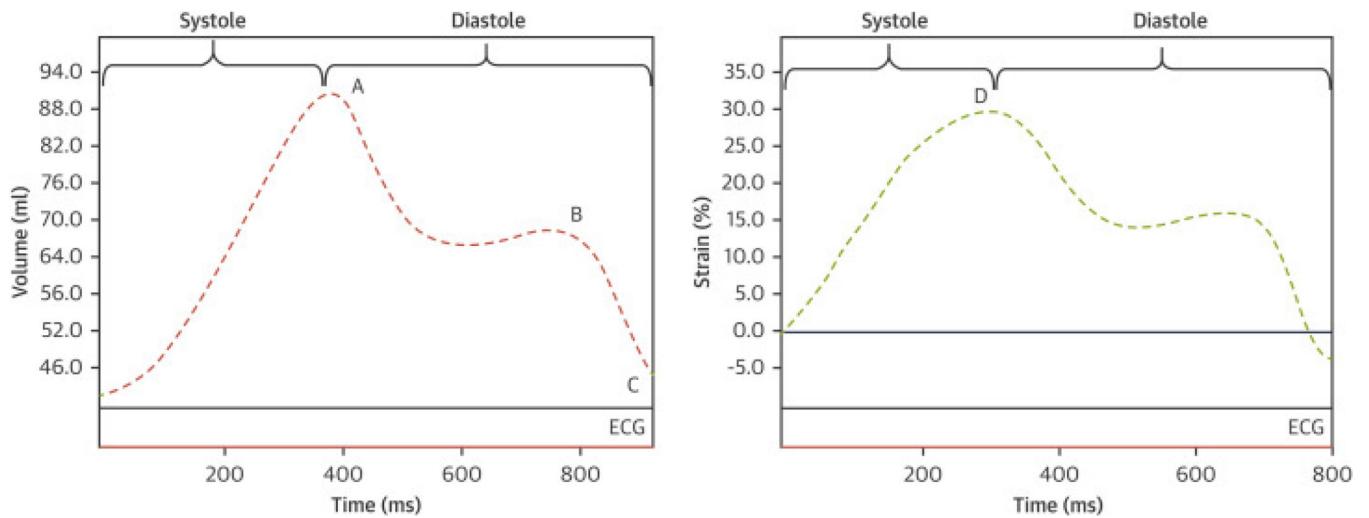
FIGURE 1. Feature Tracking Derived Left Atrial Volume and Strain Curves
(**Left**) Changes in LA volume during cardiac cycle (ventricular systole and diastole). Maximum, pre-atrial contraction, and minimum LA volumes (**points A, B, and C**, respectively) were measured using LA volume curve. (**Right**) Changes in LA longitudinal strain during cardiac cycle. **Point D** indicates peak longitudinal strain. LA = left atrium.
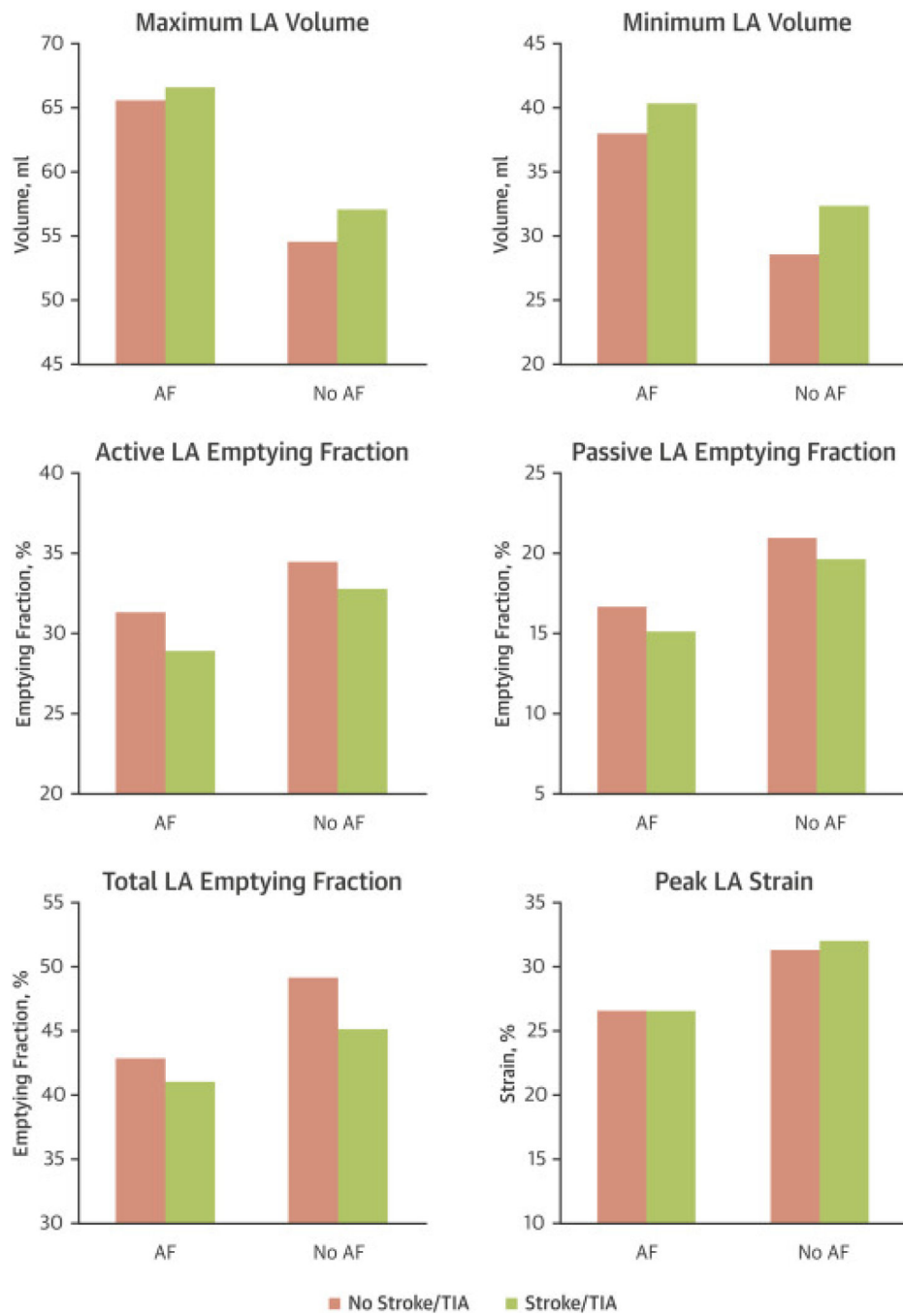
FIGURE 2. Atrial Variables by Strata of Atrial Fibrillation and Stroke/TIA

Bars demonstrate the means of each measured atrial variable by strata of atrial fibrillation and ischemic cerebrovascular events. AF = atrial fibrillation; LA = left atrial; TIA = transient ischemic attack.
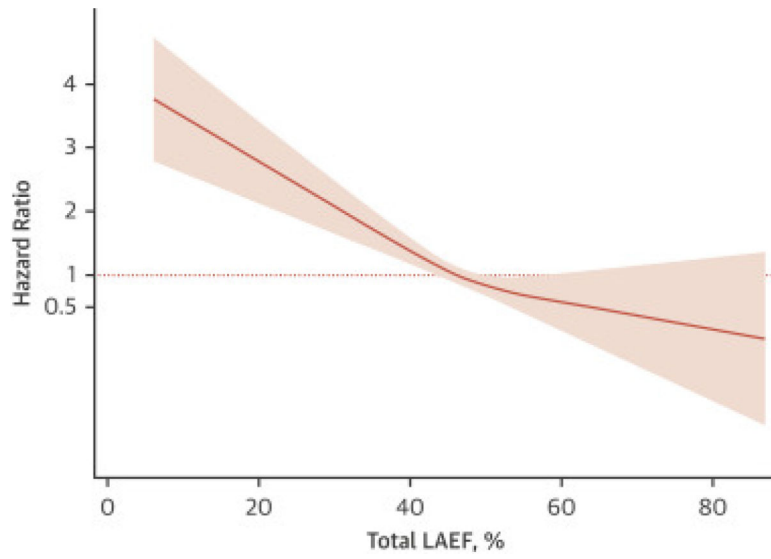
FIGURE 3. Total Left Atrial Emptying Fraction and Incident Ischemic Cerebrovascular Events
The plot demonstrates the results of a restricted cubic spline model. The **pink area above and below the pink line** indicates the 95% confidence interval.
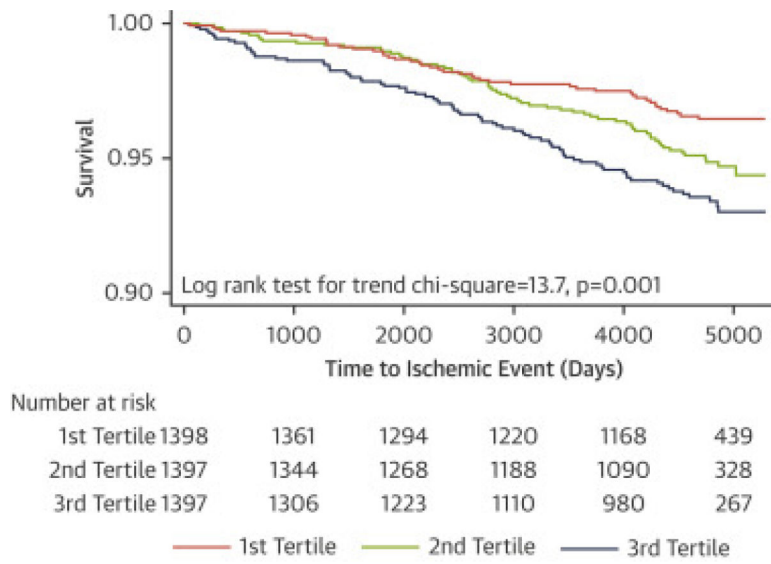
FIGURE 4. Kaplan-Meier Event-Free Survival Curves

Kaplan-Meier survival curves showing the event-free survival of participants based on tertiles of total left atrial emptying fraction. The first tertile includes participants with the highest total LAEF, and the third tertile includes participants with the lowest total LAEF. LAEF = left atrial emptying fraction.
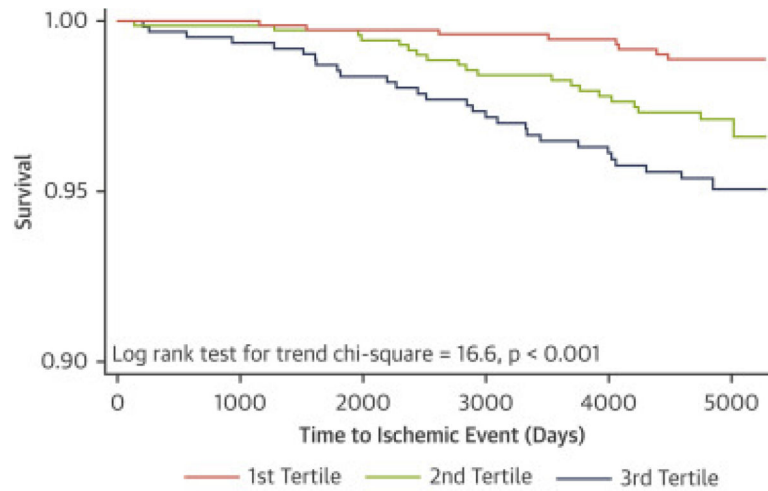
FIGURE 5. Kaplan-Meier Event-Free Survival Curves in Individuals With CHA$_2$DS$_2$-VASc Score   1

Kaplan-Meier survival curves show the event-free survival of participants based on tertiles of total left atrial emptying fraction. The first tertile includes participants with the highest total LAEF, and the third tertile includes participants with the lowest total LAEF. CHA$_2$DS$_2$-VASc = congestive heart failure, Hypertension, Age   75 years, Diabetes mellitus, Prior stroke, transient ischemic attack [TIA], or thromboembolism, Vascular disease, Age 65–74 years, Sex category [female]); other abbreviations as in Figure 4.
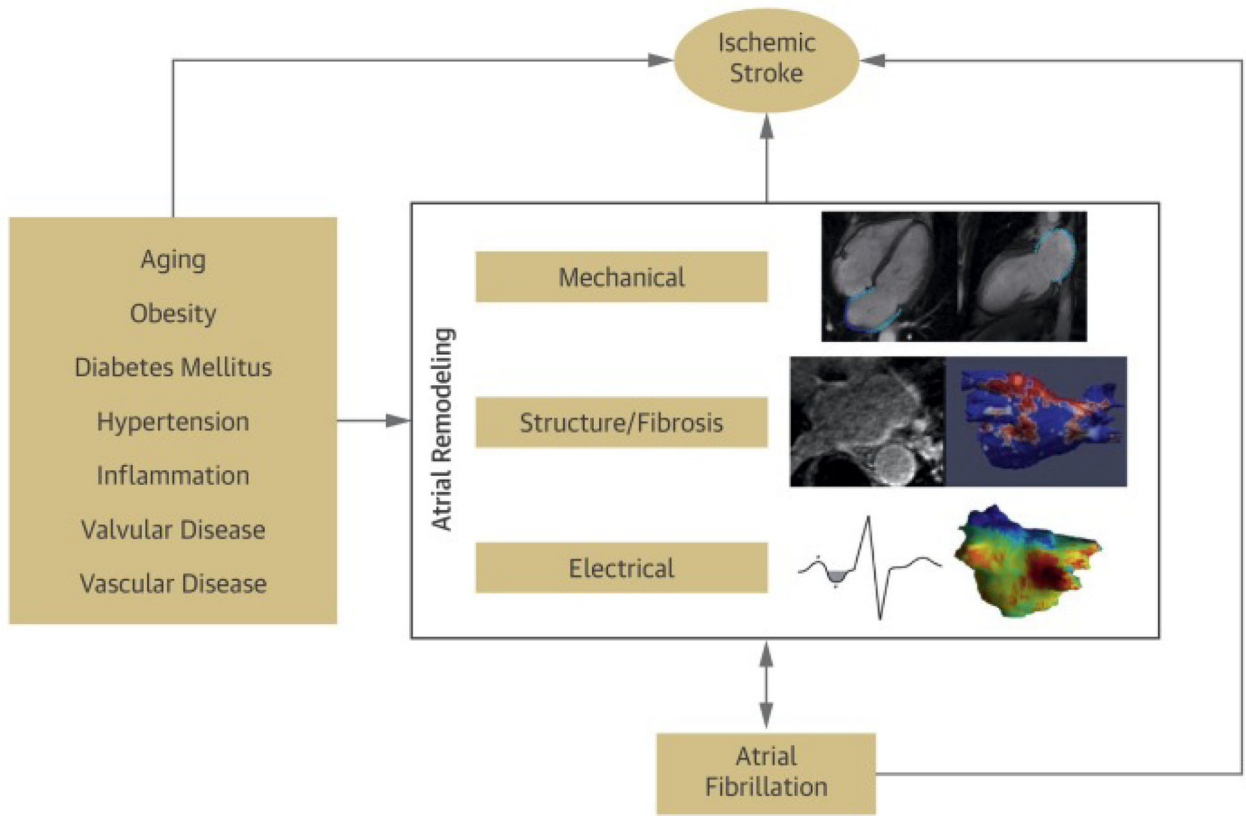
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Central Illustration. Factors leading to LA Remolding and Their Relationships to Ischemic Stroke

Shared risk factors results in mechanical, structural, and electrical LA remodeling. Electrical changes promote AF development which also worsens LA remodeling. Mechanical changes increase blood stasis and risk of thromboembolism.

Table 1.

Baseline Characteristics of Study Participants With and Without Cerebrovascular Events During the Follow-Up Period

Empty Cell	No Ischemic CVE (n = 4,068)	Ischemic CVE (n = 193)	p Value
Age, yrs	61.2 ± 10.0	66.5 ± 9.2	<0.001
Male	1,922 (47.2)	98 (50.8)	0.337
Race/ethnicity			0.003
Caucasian	1,599 (39.3)	78 (40.4)	
Chinese	510 (12.5)	9 (4.7)	
African American	1,071 (26.3)	50 (25.1)	
Hispanic	888 (21.8)	56 (29.0)	
Body mass index, kg/m^2	27.8 ± 5.0	28.7 ± 4.7	0.008
Cholesterol, mg/dl			
Total	194.4 ± 35.4	194.1 ± 36.7	0.927
LDL	117.3 ± 31.1	117.5 ± 31.0	0.936
HDL	51.3 ± 14.9	47.9 ± 13.8	0.002
Triglyceride	129.8 ± 81.1	149.1 ± 137.3	0.002
Cigarette smoking			0.171
Never	2,077 (51.2)	94 (49.0)	
Former	1,463 (36.1)	65 (33.8)	
Current	516 (12.7)	33 (17.2)	
Diabetes mellitus	504 (12.4)	41 (21.4)	<0.001
Resting heart rate	63.0 ± 9.4	63.5 ± 9.5	0.446
Blood pressure, mm Hg			
Systolic	125.2 ± 21.3	136.8 ± 21.9	<0.001
Diastolic	71.8 ± 10.3	74.8 ± 11.0	<0.001
Antihypertensive use	1,415 (34.8)	95 (49.5)	<0.001
Statin use	589 (14.5)	30 (15.6)	0.192
Developed atrial fibrillation	505 (12.4)	58 (30.7)	<0.001
LV mass, g	145.7 ± 39.4	157.9 ± 42.7	<0.001
LV ejection fraction, %	68.9 ± 7.4	68.6 ± 7.7	0.522
PTFV$_1$ >4,000, ms*μV	101 (2.5)	11 (5.7)	0.007
Log (NT-proBNP)	3.9 ± 1.2	4.3 ± 1.2	<0.001

CVE = cerebrovascular events; HDL = high density lipoprotein; LDL = low density lipoprotein; LV = left ventricle; NT-proBNP = N-terminal pro–B-type natriuretic peptide; PTFV$_1$ = P-wave terminal force in lead V$_1$.

Table 2.

Baseline Left Atrial Volumes and Function in Participants With and Without Incident Cerebrovascular Events

Empty Cell	No Ischemic CVE (n = 4,068)	Ischemic CVE (n = 193)	p Value
$LAVI_{max}$, ml/m^2	30.1 ± 9.7	32.4 ± 13.2	0.002
$LAVI_{min}$, ml/m^2	15.9 ± 6.6	18.4 ± 10.0	>0.001
Passive LAEF, %	20.4 ± 9.1	18.6 ± 8.2	0.009
Active LAEF, %	34.0 ± 10.0	31.3 ± 11.3	<0.001
Total LAEF, %	47.6 ± 9.9	43.9 ± 11.0	<0.001
LA Strain, %	30.6 ± 12.2	30.8 ± 14.8	0.805

Values are mean ± SD.

LA = left atrium; LAEF = left atrial emptying fraction; $LAVI_{max}$ = maximum left atrial volume index; $LAVI_{min}$ = minimum left atrial volume index; other abbreviations as in Table 1.

Table 3.

Association Between Left Atrial Volume and Function and Incident Ischemic Cerebrovascular Event

Empty Cell	Model 1		Model 2		Model 3	
	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
$LAVI_{max}$, ml/m^2	1.12 (0.98–1.28)	0.100	1.02 (0.88–1.18)	0.769	1.06 (0.92–1.21)	0.412
$LAVI_{min}$, ml/m^2	1.18 (1.04–1.34)	0.009	1.09 (0.96–1.24)	0.183	1.10 (0.97–1.27)	0.134
Passive LAEF, %	0.93 (0.80–1.08)	0.351	0.97 (0.83–1.13)	0.688	0.96 (0.83–1.12)	0.626
Active LAEF, %	0.84 (0.73–0.97)	0.018	0.88 (0.76–1.01)	0.074	0.87 (0.75–1.01)	0.057
Total LAEF, %	0.80 (0.69–0.92)	0.002	0.85 (0.74–0.98)	0.027	0.83 (0.72–0.96)	0.013
LA Strain, %	1.06 (0.94–1.21)	0.308	1.11 (0.98–1.26)	0.088	1.09 (0.97–1.24)	0.150

Model 1 is adjusted for age, sex, ethnicity, body mass index, cigarette smoking, systolic and diastolic blood pressures, use of antihypertension medications, total cholesterol, high-density lipoprotein, statin use, diabetes mellitus, and left ventricular mass. Model 2 consists of variables in model 1 and interim incident atrial fibrillation as a time-dependent covariate. Model 3 consists of variables in model 1 and atrial fibrillation as a time-fixed covariate. Hazard ratios were calculated according to ±SD changes in LA variables.

CI = confidence interval; other abbreviations as in Table 2.