Relation of Left Atrial Dysfunction to Ischemic Stroke in Patients With Coronary Heart Disease (from the Heart and Soul Study)

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This study sought to determine whether left atrial (LA) dysfunction independently predicts ischemic stroke. Atrial fibrillation (AF) impairs LA function and is associated with ischemic stroke. However, ischemic stroke frequently occurs in patients without known AF. The direct relation between LA function and risk of ischemic stroke is unknown. We performed transthoracic echocardiography at rest in 983 subjects with stable coronary heart disease. To quantify LA dysfunction, we used the left atrial function index (LAFI), a validated formula incorporating LA volumes at end-atrial systole and diastole. Cox proportional hazards models were used to evaluate the association between LAFI and ischemic stroke or transient ischemic attack (TIA). Over a mean follow-up of 7.1 years, 58 study participants (5.9\%) experienced an ischemic stroke or TIA. In patients without known baseline AF or warfarin therapy (n = 893), participants in the lowest quintile of LAFI had >3 times the risk of ischemic stroke or TIA (hazard ratio 3.3, 95\% confidence interval 1.1 to 9.7, p = 0.03) compared with those in the highest quintile. For each standard deviation (18.8 U) decrease in LAFI, the hazard of ischemic stroke or TIA increased by 50\% (hazard ratio 1.5, 95\% confidence interval 1.0 to 2.1, p = 0.04). Among measured echocardiographic indexes of LA function, including LA volume, LAFI was the strongest predictor of ischemic stroke or TIA. In conclusion, LA dysfunction is an independent risk factor for stroke or TIA, even in patients without baseline AF. Published by Elsevier Inc. (Am J Cardiol 2014;113:1679–1684)

An estimated 800,000 Americans experience a new or recurrent stroke each year.\textsuperscript{1} Atrial fibrillation (AF) or atrial flutter is an independent risk factor for ischemic stroke, increasing risk by fivefold across all age groups.\textsuperscript{2} However, only an estimated 1 of 6 ischemic strokes is associated with known AF;\textsuperscript{3} and a definite cause of stroke often cannot be determined.\textsuperscript{5} Left atrial (LA) dysfunction is an important predictor of AF\textsuperscript{2} and CHADS\textsubscript{2} scores in patients with AF,\textsuperscript{6} but its relation with ischemic stroke in the absence of AF remains unknown. Previous studies demonstrate that larger LA size is significantly associated with higher rates of ischemic stroke,\textsuperscript{7,8} even in patients without known AF.\textsuperscript{9} The left atrial function index (LAFI) is a rhythm-independent measure of atrial function that incorporates analogues of cardiac output, LA reservoir function, and LA size.\textsuperscript{10} The aim of this study was to determine whether LA dysfunction is an independent risk factor for incident ischemic stroke and transient ischemic attack (TIA).

Methods

We evaluated patients from the Heart and Soul Study, a prospective cohort study designed to study the relations between psychosocial factors and adverse outcomes in outpatients with stable coronary heart disease (CHD). A detailed description of the recruitment process has been described previously.\textsuperscript{11} From September 2000 to December 2002, a total of 1,024 outpatients with stable CHD were enrolled. We recruited 240 patients from 9 public health clinics in the Community Health Network of San Francisco, 346 from the University of California, San Francisco Medical Center, and 438 from the San Francisco or Palo Alto Veterans Affairs Medical Centers. Eligible participants met ≥1 of the following inclusion criteria: (1) history of myocardial infarction, (2) evidence of at least 50\% stenosis in ≥1 coronary vessels by angiogram, (3) exercise-induced ischemia by treadmill electrocardiogram or nuclear perfusion stress imaging, or (4) a history of coronary revascularization. We excluded subjects with
a history of myocardial infarction within the previous 6 months, with an inability to walk 1 block, and who were planning to move out of the local area within 3 years. Of the 1,024 original study subjects, we excluded 37 with missing echocardiographic data and 4 with missing outcome data, leaving 983 participants for this analysis. Our protocol was approved by the governing institutional review boards, and all participants provided written informed consent.

We performed transthoracic echocardiography at rest using an Acuson Sequoia ultrasound system (Siemens Medical Solutions, Mountain View, California) at the baseline visit for all study participants. The Heart and Soul Study protocol for echocardiography has been described previously. Briefly, 1 of 2 trained technicians performed the echocardiography using a standard protocol, with participants in the left lateral recumbent and supine positions. The borders of the LA consisted of the walls of the LA and a line drawn across the mitral annulus. If seen, the LA appendage was excluded from measurement. To measure LA size, we used LA volume index (left atrial end-systolic volume index [LAESVI]), which is recommended by the American Society of Echocardiography. LAESVI was calculated by dividing LA end-systolic volume by body surface area. LA size was categorized as follows based on standard reference limits from the American Society of Echocardiography: normal (<28 ml/m²), mild-to-moderate dilation (28 to 40 ml/m²), and severe dilation (>40 ml/m²).

The derivation and validation of LAFI have been previously described. The LAFI (see Box 1) is a ratio that incorporates analogues of cardiac output (left ventricular outflow tract velocity-time integral), LA reservoir function (total emptying fraction), and LA size (LAESVI). A single cardiologist (NBS) blinded to laboratory and clinical information interpreted all echocardiographic measurements used to calculate LAFI. The reproducibility of LAFI as performed by this cardiologist has been previously described with Bland-Altman analyses, which revealed no significant variation.

The outcome was time to first ischemic stroke or TIA. After the baseline assessment, we contacted study participants or their proxies annually by telephone and asked specifically about stroke and other hospitalizations. Stroke was defined as a new neurologic deficit not known to be secondary to brain trauma, tumor, infection, or other cause, based on the WHO MONICA (World Health Organization Monitoring of Trends and Determinants in Cardiovascular Disease) criteria. All stroke outcomes were subtyped as hemorrhagic, ischemic, or procedure related and were confirmed by computed tomography or magnetic resonance imaging in 84% of cases. Hemorrhagic and procedure-related strokes were excluded in this study. TIA was defined as a focal neurologic deficit lasting >30 seconds but ≤24 hours, with rapid evolution of symptoms to the maximal level of deficit in ≤5 minutes and with subsequent complete resolution. Two independent and blinded adjudicators reviewed medical records for any reported events. If the adjudicators agreed, their classification was binding. If the adjudicators disagreed, they reconsidered their classification and requested consultation from a third blinded adjudicator if needed.

At the baseline visit, age, gender, race, and medical history were determined by self-report. Patients were instructed to bring their medication bottles to the study appointment, and study personnel recorded all current medications. We measured height and weight and calculated body mass index in kg/m². Systolic and diastolic blood pressures were measured in the supine position after 5 minutes of rest. We measured low-density lipoprotein, high-density lipoprotein, and N-terminal pro-B-type natriuretic peptide levels in fasting blood samples drawn at the baseline study appointment. N-terminal pro-B-type natriuretic peptide was log transformed to meet the assumption of linearity. To detect baseline AF, standard 12-lead electrocardiography was performed on all subjects at the time of enrollment.

Using transthoracic echocardiograms at rest, we measured the following additional variables: LA ejection fraction, LA ejection volume, LA end-diastolic volume index, left ventricular ejection fraction, left ventricular end-diastolic volume index, left ventricular mass index, pulmonary artery systolic pressure, pulmonary artery diastolic pressure, diastolic dysfunction as 1 of 3 categories (none, impaired relaxation, and pseudonormal or restrictive), and pulmonary vascular resistance. These additional echocardiographic variables have been defined previously.

The aim of this study was to determine whether LAFI is independently associated with ischemic stroke or TIA. Participants were divided into quintiles based on their LAFI. We compared differences in baseline characteristics across quintiles using chi-square tests for categorical variables and 1-way analysis of variance for continuous variables. We performed multivariate Cox regression to compare the hazard of ischemic stroke or TIA across quintiles of LAFI. Using the same models, we also assessed the hazard of ischemic stroke or TIA per standard deviation decrease of LAFI. We also performed a sensitivity analysis in which we excluded patients with baseline AF.

We also sought to determine the independent association of several quantitative echocardiographic LA variables (LAESVI, LA end-diastolic volume index, LA ejection fraction, LA ejection volume, and LAFI) with the hazard of stroke or TIA, after adjusting for age, gender, race, and stroke or TIA risk factors. Exploratory analysis indicated very high collinearity of these measurements with each other and with LAFI. Using a series of multivariate analysis, we compared the highest and lowest quintiles of each echocardiographic LA variable to determine their independent associations with the hazard of stroke.

Assessment of the proportional hazards assumption using Schoenfeld residuals revealed no violations. We used Wald tests to check for interactions of LAFI with LAESVI.
in age-adjusted and multivariable-adjusted models. We used C statistics and chi-square likelihood ratio testing to compare the discrimination of LAFI and LA volume index within categories of LA size. All analyses were conducted using Stata, version 12.0 (StataCorp LP, College Station, Texas).

Results

Nine hundred eighty-three participants were included in this study. LAFI was normally distributed, with a mean baseline value of 40.1 ± 18.8 U. Baseline characteristics of participants across quintiles of LAFI are displayed in
Table 1. Compared with participants with high LAFI, those with low LAFI were older and more likely to have a history of congestive heart failure, higher levels of N-terminal pro-B-type natriuretic peptide, and AF on baseline electrocardiography. They were also more likely to be taking warfarin, renin-angiotensin system inhibitors, and loop or thiazide diuretics but less likely to be taking aspirin. LAFI was also significantly associated with echocardiographic characteristics as listed in Table 2.

During a median follow-up of 8.4 years, 58 subjects experienced an ischemic stroke (n = 40) or TIA (n = 18). Subjects with incident stroke or TIA had reduced LAFI compared with subjects who did not (mean 35.0 ± 18.0 vs 40.4 ± 18.8 U, respectively, p = 0.03). Ischemic stroke or TIA event rates increased from 5.3 per 1,000 person-years in the highest quintile to 15.6 per 1,000 person-years in the lowest quintile of LAFI (Table 3). Kaplan-Meier survival estimates show the event-free survival curve from the lowest LAFI quintile separating from the other curves within the first 3 years (Figure 1).

Table 3. Age-adjusted association between quintile of left atrial (LA) function index and stroke or transient ischemic attack (TIA)

<table>
<thead>
<tr>
<th>LA Functional Index</th>
<th>Person-Time (yrs)</th>
<th>Events</th>
<th>Event Rate (per 1,000 Person-Years)</th>
<th>Age-Adjusted HR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quintile V (54.6–160 U)</td>
<td>1,524</td>
<td>6</td>
<td>2</td>
<td>5.3 REF</td>
<td>REF</td>
</tr>
<tr>
<td>Quintile IV (43.1–54.6 U)</td>
<td>1,440</td>
<td>9</td>
<td>4</td>
<td>9.0 1.7 (0.7–4.1)</td>
<td>0.23</td>
</tr>
<tr>
<td>Quintile III (34.2–43.1 U)</td>
<td>1,460</td>
<td>2</td>
<td>2</td>
<td>2.7 0.5 (0.2–1.7)</td>
<td>0.29</td>
</tr>
<tr>
<td>Quintile II (24.3–34.2 U)</td>
<td>1,345</td>
<td>8</td>
<td>6</td>
<td>10.4 1.9 (0.8–4.6)</td>
<td>0.14</td>
</tr>
<tr>
<td>Quintile I (0–24.3 U)</td>
<td>1,222</td>
<td>15</td>
<td>4</td>
<td>15.6 2.6 (1.1–6.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Total</td>
<td>6,991</td>
<td>58</td>
<td>8.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; REF = reference.

In subjects without known baseline AF or warfarin therapy (n = 893), participants in the lowest quintile of LAFI had a significantly increased risk of ischemic stroke or TIA (hazard ratio 3.3, 95% confidence interval 1.1 to 9.7, p = 0.03) compared with those in the highest quintile of LAFI (Table 4). When LAFI was analyzed as a continuous variable in the entire cohort, each standard deviation (18.8 U) decrease below the mean was associated with a 50% increase in risk of stroke or TIA risk (hazard ratio 1.5, 95% confidence interval 1.0 to 2.1, p = 0.04). In sequential multivariate models of LAESVI, LA end-diastolic volume index, LA ejection fraction, LA ejection volume, and LAFI, only LAFI was independently associated with stroke or TIA.

Discussion

In a prospective cohort study of 983 outpatients with preexisting CHD, we investigated the association between LA dysfunction, as measured by LAFI, and risk of incident ischemic stroke or TIA. We demonstrated a significant

![Figure 1. Proportion without ischemic stroke or TIA, stratified by quintiles of LAFI. Kaplan-Meier plot of time to ischemic stroke or TIA in subjects with stable CHD, stratified by quintiles of LAFI. The rate of stroke or TIA was highest in subjects with the lowest quintile (red line) of LA function and lowest in subjects in the highest quintile (black line) of LA function (log-rank p = 0.005).](image-url)
Arrhythmias and Conduction Disturbances/Left Atrial Dysfunction and Ischemic Stroke

Table 4
Multivariate survival analysis between quantitative left atrial (LA) echocardiographic parameters and ischemic stroke or transient ischemic attack in patients without known atrial fibrillation or flutter or warfarin therapy (n = 893)

<table>
<thead>
<tr>
<th>LA Echocardiographic Variable</th>
<th>Mean ± SD</th>
<th>Quintile</th>
<th>HR (95% CI)</th>
<th>p Value</th>
<th>Per SD</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA end-diastolic volume index (ml/m²)</td>
<td>14.5 ± 7.2</td>
<td>V vs I</td>
<td>1.7 (0.7–4.6)</td>
<td>0.26</td>
<td>Increase</td>
<td>1.3 (1.0–1.8)</td>
<td>0.09</td>
</tr>
<tr>
<td>LAESVI (ml/m²)</td>
<td>31.9 ± 10.3</td>
<td>V vs I</td>
<td>1.7 (0.7–4.1)</td>
<td>0.26</td>
<td>Increase</td>
<td>1.3 (1.0–1.8)</td>
<td>0.06</td>
</tr>
<tr>
<td>LA ejection fraction (%)</td>
<td>55.4 ± 11.6</td>
<td>I vs V</td>
<td>1.9 (0.7–4.7)</td>
<td>0.19</td>
<td>Decrease</td>
<td>1.2 (0.8–1.6)</td>
<td>0.37</td>
</tr>
<tr>
<td>LA ejection volume index (ml/m²)</td>
<td>17.4 ± 5.9</td>
<td>I vs V</td>
<td>0.7 (0.3–1.8)</td>
<td>0.50</td>
<td>Decrease</td>
<td>0.8 (0.6–1.1)</td>
<td>0.13</td>
</tr>
<tr>
<td>LAFI (U)</td>
<td>41.9 ± 18.0</td>
<td>I vs V</td>
<td>3.3 (1.1–9.7)</td>
<td>0.03</td>
<td>Decrease</td>
<td>1.5 (1.0–2.1)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Models are adjusted for age, gender, white race, and ischemic stroke risk factors (previous stroke or TIA, hypertension, hyperlipidemia, diabetes, and current tobacco use).
CI = confidence interval; HR = hazard ratio; SD = standard deviation.
* Patients were excluded if they had baseline AF or atrial flutter (by history and electrocardiography) or warfarin use.

association between LA dysfunction and risk of incident ischemic stroke or TIA, including in subjects without baseline AF. The risk of ischemic stroke or TIA was almost threefold higher in participants with LAFI in the lowest versus highest quintiles. LAFI was a stronger predictor than other echocardiographic measures of LA volume and function, including LA volume index.

The association between LA size, LA function, AF, and ischemic stroke risk is incompletely understood, but several possible mechanisms may explain this complex relation. First, LA dysfunction may result in diminished atrial contractility, promoting hemostasis, thrombosis, and cardioembolic stroke. Patients with stroke have decreased fractional area change in the LA and LA appendage compared with controls. Elevated LA pressure decreases flow velocity in the LA appendage. Spontaneous echo contrast, a marker of blood stasis, is associated with LA dysfunction. We have previously demonstrated that LAFI predicts heart failure hospitalizations in patients with preserved ejection fraction in this cohort.

Second, LA dysfunction may be a marker for other ischemic stroke risk factors, irrespective of stroke cause. LA reservoir dysfunction is associated with subclinical cerebrovascular disease, independent of other cardiovascular risk factors such as AF, and with acute ischemic strokes in the absence of AF. LA dysfunction may therefore be a global marker of atherosclerotic burden, indicating increased risk for large or small artery strokes. Consistent with this hypothesis, most patients with an implantable device have 0 AF burden 30 days before an ischemic stroke or TIA, implying mechanisms other than cardioembolism.

Third, the relation between LA dysfunction and ischemic stroke may be explained through AF, acting as either a confounder or mediator. Previous studies have shown that LA enlargement precedes and increases the risk of AF. LA remodeling and dysfunction may be accompanied by progressive interstitial fibrosis, comprising an arrhythmogenic substrate for the development of AF. More recently, LA reservoir function has been shown to increase the likelihood of incident AF, independent of LA volume. Moreover, AF burden is proportional to the degree of LA dysfunction, and LA dysfunction may be present in patients with AF despite normal LA size and sinus rhythm. However, increased LA volume was previously found to be associated with first-time ischemic strokes in elderly patients without AF. Alternatively, LA dysfunction may be a marker of occult atrial tachyarrhythmias. Healey et al. have recently shown that subclinical atrial tachyarrhythmias occurred frequently in patients with pacemakers and are associated with an increased risk of ischemic stroke and cardioembolism.

Could substrate rather than rhythm be used for stroke risk prediction? We have previously shown in this cohort that CHADS2 scores are correlated with stroke risk in the absence of AF. Given the improvement in safety profiles of the new oral anticoagulants, the risk threshold for anticoagulation therapy of patients will likely decrease. Measurement of LA function with LAESVI and tissue Doppler velocity using echocardiography has previously been shown to rule out paroxysmal AF in patients presenting with stroke or TIA. The utility of substrate based risk stratification merits further study in larger cohorts.

There are several limitations to our study. This cohort was composed of primarily Caucasian male patients with stable CHD, which may limit generalizability. Also, this study was not powered to determine whether LA dysfunction is associated with specific stroke subtypes, such as cardioembolic or lacunar. The modest number of stroke events limits the ability to create large multivariate models or robust clinical prediction rules because of the risk of model overfitting, particularly because baseline clinical and echocardiographic variables have a high degree of collinearity. Last, as mentioned previously, AF was determined by baseline electrocardiography, and, therefore, some patients with previous AF or paroxysmal AF may have been misclassified.

Disclosures

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