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

Jonathan M. Wong, MD[a,b], Christine C. Welles, MD[c,d], Farnaz Azarbal, MD[e], Mary A. Whooley, MD[c,d,f], Nelson B. Schiller, MD[c,g], and Mintu P. Turakhia, MD, MAS[e,h,*]

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.[1] Atrial fibrillation (AF) or atrial flutter is an independent risk factor for ischemic stroke, increasing risk by fivefold across all age groups.[2] However, only an estimated 1 of 6 ischemic strokes is associated with known AF,[3] and a definite cause of stroke often cannot be determined.[4] Left atrial (LA) dysfunction is an important predictor of AF[5] and $CHADS_2$ scores in patients with AF,[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,[7,8] even in patients without known AF.[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.[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.[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]Doris Duke Clinical Research Fellowship Program, University of California, San Francisco, California; [b]Department of Medicine, California Pacific Medical Center, San Francisco, California; [c]Veterans Affairs Medical Center, San Francisco, California; Departments of [d]Medicine, [f]Epidemiology & Biostatistics, and [g]Division of Cardiology, University of California, San Francisco, San Francisco, California; [e]Division of Cardiovascular Medicine, Department of Medicine, Stanford University, Stanford, California; and [h]Veterans Affairs Palo Alto Health Care System, Palo Alto, California. Manuscript received February 8, 2014; revised manuscript received and accepted February 21, 2014.

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*Corresponding author: Tel: (650) 723-7111; fax (866) 756-3025.
E-mail address: mintu@stanford.edu (M.P. Turakhia).

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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.[12] 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.[13] 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/m^2), mild-to-moderate dilation (28 to 40 ml/m^2), and severe dilation (>40 ml/m^2).

The derivation and validation of LAFI have been previously described.[10] 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.[10]

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.[14] 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.

Box 1: Left atrial function index (LAFI)

$$\text{LAFI} = \frac{\text{Left atrial emptying fraction} \times \text{LVOT VTI (cm)}}{\text{LAESVI (cc/m}^2\text{)}}$$

LVOT VTI = velocity-time integral of the left ventricular outflow tract (cm)

LAESVI = maximal left atrial volume in end-systole (cc) indexed to body surface area (m^2)

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/m^2. 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.[15−17]

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.[18] We used Wald tests to check for interactions of LAFI with LAESVI