Left Atrial Strain Is Reduced in Patients with Atrial Fibrillation, Stroke or TIA, and Low Risk CHADS₂ Scores

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Background: Left atrial (LA) strain as a marker for discrimination of risk for stroke and transient ischemic attack (TIA) in patients with atrial fibrillation and low-risk CHADS₂ scores (≤1) has yet to be examined.

Methods: Patients with atrial fibrillation, stroke or TIA, and CHADS₂ scores ≤ 1 before their events were identified retrospectively from a large single-center stroke registry and compared with age-matched and gender-matched controls. Antihypertensive use and echocardiographic parameters including chamber volumes and left ventricular mass and LA peak negative and positive strain and strain rate were compared between groups.

Results: Fifty-seven patients meeting entry criteria were identified. Patients demonstrated significantly lower left ventricular ejection fractions, larger LA dimensions, and larger LA volume indexes (24.4 ± 11.9 vs 32.3 ± 13.3 mL/m², P = .012) compared with controls. Both peak negative LA strain (–3.2 ± 1.2% vs –6.9 ± 4.2%, P < .001) and peak positive LA strain (14 ± 11% vs 25 ± 12%, P < .001) were significantly reduced in patients compared with controls. Peak negative LA strain was significantly associated with stroke by binary logistic regression (odds ratio, 2.15; P < .001).

Conclusions: In patients with low-risk CHADS₂ scores, atrial fibrillation, and stroke or TIA, reduced LA strain is a potentially sensitive maker for increased risk for stroke or TIA. These results suggest that LA strain may have potential as a tool for helping guide the decision for or against oral anticoagulation in this group of patients. (J Am Soc Echocardiogr 2012;25:1327-32.)

Keywords: Echocardiography, Embolic stroke, Atrial fibrillation, Anticoagulation

Since its emergence as an effective prophylaxis against cardioembolic stroke in patients with atrial fibrillation (AF), oral anticoagulation has endured as a therapeutic triumph. Warfarin decreases annual stroke rates for patients with nonrheumatic AF from 4.5% to 1.4% compared with placebo,¹ for an overall stroke reduction of 60%.²,³ Risk for thromboembolism, however, is not evenly distributed among all patients with AF. In the absence of concomitant risk factors, the incidence of stroke in patients with AF is similar to that in the general population.⁴-⁶ As the sum of stroke risk factors increases, stroke frequency increases proportionately.¹

This heterogeneity of risk has led to the promulgation of numerous strategies for risk stratification,¹,⁶,¹⁵ in which established stroke risk factors (heart failure, hypertension, older age, diabetes, and previous stroke or transient ischemic attack [TIA]) are added together to produce a total point score. Although risk increases with higher scores, stroke rates in lower risk patients vary up to fourfold depending on which scoring system is applied.⁶,¹⁶ Perhaps as a way to resolve the uncertainty generated by such variable results, current guidelines recommend that anticoagulation or antiplatelet therapy be individualized for patients with AF and only one other stroke risk factor.²² Although severe left ventricular (LV) dysfunction is recognized as a significant adverse predictor, no scheme at present incorporates any other marker of cardiac structure or function. Although elevated left atrial (LA) dimension is a common finding in AF and is associated with increased risk for ischemic stroke,²² its utility as an independent predictor of thromboembolic stroke risk in the setting of AF remains controversial.¹⁴

We hypothesized that the addition of a quantitative functional marker of thromboembolic risk to current classification schemes might increase their robustness as a guideline for anticoagulation and in particular improve decision making for low-risk patients. We further hypothesized that LA strain would be a strong candidate for such a marker.¹³,¹⁴ We used a widely accepted classification system, the CHADS₂ score, to identify a cohort of patients with AF at relatively low risk for stroke or TIA. We compared echocardiographic dimensions, systolic function, and LA strain in these patients with these values in matched controls to determine whether that measure or any other echocardiographic variable would produce a significant difference between the two groups.

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1327
diagnosis of stroke or TIA was confirmed by clinical assessment of a board-certified neurologist combined with computed tomographic or magnetic resonance imaging findings in 5,490 patients; stroke or TIA was ruled out in 1,163 patients. A history of paroxysmal AF or electrocardiographic evidence of AF within 24 hours of the event was confirmed in 615 patients. Within this group, 75 patients with imaging or clinical findings suggestive of thromboembolic stroke or TIA, CHA2DS2 scores ≤ 1 before the index events, and technically adequate transthoracic echocardiograms within 24 hours of presentation were identified retrospectively. Five patients whose echocardiograms were technically inadequate for strain analysis were excluded. Because the following conditions independently qualify patients for oral anticoagulation or produce LA dysfunction,5 patients with LV ejection fractions < 35% (n = 8), mitral stenosis (n = 4), or the presence of a prosthetic heart valve or valve repair (n = 6) were excluded, leaving 57 patients available for analysis. Controls were selected from patients within the registry (n = 48) or the inpatient echocardiography laboratory database (n = 9) with electrocardiographically documented AF or documented histories of paroxysmal AF with otherwise identical inclusion criteria but without evidence of history or stroke or TIA or any history of oral anticoagulation before the index echocardiographic assessment. Patients and controls were matched for sex, age (± 3 years), and aspirin use before presentation. Patients underwent standard, digitized echocardiography within 72 hours of presentation. The study was approved by the Hartford Hospital Institutional Review Board.

Data

Age, sex, international normalized ratio (INR), and CHADS2 and CHA2DS2-VASc scores immediately before stroke or TIA were recorded. CHADS2 scores were calculated by adding 1 point for congestive heart failure, hypertension, age ≥ 75 years, and diabetes mellitus,20 and CHA2DS2-VASc scores were compiled by adding 1 point for female sex, documented vascular disease, or age 64 or greater. Body surface area was recorded for each patient and control. All echocardiographic images were obtained from Siemens Sequoia 512 (Siemens Medical Solutions USA, Inc, Mountain View, CA), Philips iE33 (Philips Medical Systems, Andover, MA), or Philips 7500 (Philips Medical Systems) sonographs, translated into Digital Imaging and Communications in Medicine format, and transferred to an offline analysis system (Hearthlab; Agfa, Hackensack, NJ). Echocardiographic dimensions were measured, and LV mass index was calculated. LV ejection fraction was measured from apical four-chamber and two-chamber views using Simpson’s biplane method.25

RESULTS

The mean age of the entire cohort was 65 years (Table 1); 30 patient-control pairs (53%) were men. TIA was documented in 10% (n = 6) of patients; five patient-control pairs (9%) were classified with...
CHADS2 scores of 0. In the remaining 52 patient-control pairs, hypertension was ubiquitous and was the factor responsible for producing a CHADS2 score of 1 in all but one patient and two controls (Table 1). Mean CHA2DS2-VASc scores were higher (2.0 \pm 0.9 for both patients and controls) in large part because women constituted nearly half the study cohort. Seventy-five percent of pairs (43 of 57) were matched by both CHADS2 and CHA2DS2-VASc scores, and 30% of patients had CHA2DS2-VASc scores \( \geq 1 \). A minority of patient-control pairs (34%) were taking aspirin. Eleven patients (19%) had histories of warfarin use before stroke or TIA; in four patients, warfarin had been discontinued before a surgical procedure, the INR was \( \leq 1 \) in each patient, and the stroke occurred perioperatively. The remaining patients all presented with subtherapeutic INRs documented at the time of stroke or TIA (mean, 1.54 \pm 0.28; range, 1.06–1.81). Patients demonstrated significantly lower LV ejection fractions, larger LA dimensions, and larger LA volume indexes (LAVIs) compared with controls (Table 1). There was no significant difference in the frequency of moderate or severe mitral regurgitation or in the frequency of paroxysmal AF between groups (Table 1).

Peak negative LA strain and LA strain rate were significantly lower in controls compared with patients, and peak positive strain and strain rate were significantly higher (Table 1). Differences between patients and controls were similar for patients with permanent AF and paroxysmal AF (Table 2). All four strain indexes were weakly but significantly correlated across the entire cohort, with patients generally skewed toward the upper right end of the scatter graph (lower peak negative LA strain and higher LAVI; Table 3, Figure 2).

Binary logistic regression analyzing stroke or TIA as the dependent variable and all other significant variables as covariates revealed peak negative and positive strain as the only independent predictors of stroke. Because strain and strain rate are so highly correlated, we performed a sensitivity analysis on the initial regression model including both variables to determine what effect the elimination of strain rate would have on the remaining covariates. With or without the inclusion of strain rate, peak positive and negative strain were the only significant predictors of stroke (Table 4), with no change observed in either the odds ratios or 95% confidence intervals for those terms. The Wald scores for the remaining nonsignificant variables also remained unchanged when strain rate was removed (Table 4).

Using a cutoff value for peak negative strain of \( \leq -5.0% \), the sensitivity, specificity, positive predictive value, and negative predictive value of this variable as a potential marker stroke or TIA were calculated as 93%, 60%, 71%, and 92%, respectively.
DISCUSSION

In this retrospective, registry-based study of 57 patients with AF, documented stroke or TIA, and low-risk CHADS2 scores for stroke before their events, we found that four different indexes of LA strain were significantly decreased in patients compared with age-matched and gender-matched controls with identical CHADS2 scores. A significant association between LA strain indexes and stroke was identified by binary logistic regression, suggesting that peak negative strain might be a predictor of stroke or TIA. These results add new information to the ongoing debate surrounding optimal protection against stroke in this population.

LA strain has been shown previously to be significantly reduced in patients with AF and histories of stroke compared with patients with AF who were stroke free. In this series, however, CHADS2 scores were also significantly higher in patients with stroke, leaving open the likelihood that other factors beyond LA dysfunction contributed to stroke. In a prospective series comparing both patients with and without AF, LA strain was negatively correlated with both the presence of AF and increasing CHADS2 score in patients with AF, and lower LA strain was associated with adverse outcomes. To our knowledge, our study is the first of its kind to specifically examine the incremental thromboembolic risk conferred by reduced LA strain in patients with AF closely matched for clinical risk. Our findings suggest that reduced LA strain and strain rate may provide incremental information about stroke risk beyond the clinical factors included in the commonly accepted scoring systems and may prove superior to any alternative echocardiographic marker, such as LAVI, for that purpose.

The lower LA strain in our patients suggests that this parameter may be a marker of a direct contributor to thrombogenic risk (or both). Any hemodynamic factor that predisposes to atrial deformation will increase the likelihood of AF, and the most common contributor to LA expansion, hypertension, is itself a primary driver of stroke risk. Even in the absence of hemodynamic factors, AF alone will produce elevated LA volumes through a process of electrical and structural remodeling in sequence, followed by histologic and biochemical evidence of atrial myopathy. In our study, the correlation between increasing LA volume and decreasing LA strain suggest some degree of synergy between the two variables. Although LA volume is also a measure of such changes, and systolic strain and LAVI are both statistically correlated and mechanistically linked, our data generate the hypothesis that LA strain may provide a sensitive indicator of substrate for thrombus formation, especially in lower risk patients. Such a hypothesis will need to be tested prospectively to determine whether the sensitivity of LA strain is truly as robust as suggested by our findings. The lower specificity and positive predictive value also imply that reduced LA strain may overestimate stroke risk regardless of sensitivity and therefore should be applied to otherwise low-risk patients with caution.

Multiple functional measures of atrial function have been previously proposed, including atrial appendage flow velocity, atrial ejection force, LA emptying fraction, and LA Doppler tissue imaging velocity. As epidemiologic markers for disease, such functional measures have proven valuable in a variety of clinical settings such as diastolic heart failure and mild hypertension, although the
relationships between several of these functional measures and LAVI are often weak. LAVI was also significantly increased in patients with stroke and is easier to measure, but it does not appear to be as powerful a discriminator as LA strain. The other variables described above require intensive measurement, the presence of sinus rhythm, rigorous calculation, transesophageal echocardiography, or some combination of all three. The increasing ease with which LA strain can be measured using current technology makes it an especially attractive tool for risk assessment.

Compared with the size of previous trials of AF and stroke prevention, the small number of patients, the highly selective nature of our patients, and the single-center source in our study demand that our results be interpreted with caution. Nevertheless, the highly significant difference in all four strain parameters between patients and controls argues that our patient number is more than sufficient. Data regarding the duration of AF were not available, and it is possible that increased duration of AF could have contributed to the decreased LA strain observed in our patients with stroke. However, we have no reason to believe that duration would differ significantly in these otherwise fairly closely matched groups. The surprisingly low rate of aspirin use raises the possibility that some of these strokes might have been prevented even without oral anticoagulation. In a minority of cases, a decision for oral anticoagulation had already been made, and the occurrence of stroke or TIA in the setting of a subtherapeutic INR on admission for each of these patients vindicates that decision. Finally, a newer and equally well accepted stratification system that incorporates gender and evidence of vascular risk, the CHA2DS2-VASc score, reclassified a majority of our patients as candidates for anticoagulation. In these patients, LA strain, although still significantly reduced, would have less impact on decision making. In the remaining patients with low-risk CHA2DS2-VASc scores, LA strain measurements might be of value.

CONCLUSIONS

LA strain, however measured, appears to have the potential to discriminate between patients with AF with lower risk CHA2DS2 scores who have strokes or TIAs compared with those who do not. If validated by further investigation, this variable has the potential to aid clinical decision making with regard to anticoagulation for these patients.

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