Echocardiographic Predictors of Nonrheumatic Atrial Fibrillation

The Framingham Heart Study

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Background Although structural heart disease is often present in patients with nonrheumatic atrial fibrillation, the echocardiographic precursors of atrial fibrillation have not been reported previously. In this elderly, population-based cohort, our objective was to examine prospectively the echocardiographic predictors of nonrheumatic atrial fibrillation.

Methods and Results Subjects in the Framingham Heart Study were routinely evaluated with M-mode echocardiography; 1924 subjects, ranging in age from 59 to 90 years, comprised the population at risk. Cox proportional hazards modeling was used to analyze the association of selected echocardiographic features with atrial fibrillation risk after adjustment for age, sex, hypertension, coronary heart disease, congestive heart failure, diabetes, and valvular heart disease. During a mean follow-up interval of 7.2 years, 154 subjects (8.0%) developed atrial fibrillation. Multivariable stepwise analysis identified left atrial size (hazard ratio [HR] per 5-mm increment, 1.39; 95% confidence interval [CI], 1.14 to 1.68), left ventricular fractional shortening (HR per 5% decrement, 1.34; 95% CI, 1.08 to 1.66), and sum of septal and left ventricular posterior wall thicknesses (HR per 4-mm increment, 1.28; 95% CI, 1.03 to 1.60) as independent echocardiographic predictors of atrial fibrillation. For each of the echocardiographic predictors, risk increased progressively over successive quartiles. Moreover, risk increased markedly when highest-risk-quartile measurements for these features were present in combination; the cumulative 8-year age-adjusted atrial fibrillation rates were 7.3% and 17.0%, respectively, when one and two or more highest-risk-quartile features were present, compared with 3.7% when none was present.

Conclusions In this elderly, population-based sample, left atrial enlargement, increased left ventricular wall thickness, and reduced left ventricular fractional shortening were predictive of risk for nonrheumatic atrial fibrillation. These echocardiographic precursors offer prognostic information beyond that provided by traditional clinical atrial fibrillation risk factors. (Circulation. 1994;89:724-730.)

Key Words • atrial fibrillation • echocardiography • epidemiology

Atrial fibrillation has been shown to be associated with increased risk for cardiovascular disease morbidity and mortality. Nonrheumatic atrial fibrillation carries a nearly fivefold increased risk for stroke compared with normal sinus rhythm. Moreover, because of the sharp rise in atrial fibrillation incidence with advancing age, the proportion of strokes occurring in the setting of this dysrhythmia assumes greater magnitude in the elderly. Recent trials have demonstrated the efficacy of prophylactic anticoagulation for reducing the incidence of stroke in patients with nonrheumatic atrial fibrillation.

Identification of factors predisposing to atrial fibrillation may have implications for its prevention and may facilitate the detection of subjects most susceptible to atrial fibrillation and its sequelae. Although previous case-control studies have reported an increase in prevalence of left atrial enlargement in patients with atrial fibrillation, to the best of our knowledge, no prior study has prospectively evaluated the echocardiographic predictors of atrial fibrillation in a large population.

Between 1979 and 1981, echocardiograms were routinely obtained on original subjects of the Framingham Heart Study, a community-based, longitudinal study of men and women closely monitored for the development of cardiovascular disease. The purpose of the present investigation was to examine prospectively the echocardiographically determined structural and functional precursors of nonrheumatic atrial fibrillation.

Methods

The study sample consisted of original subjects from the Framingham Heart Study who have been followed with biennial examinations since 1948 and who were between 30 and 62 years of age at study inception. Details concerning the methods of data collection and cohort surveillance are described elsewhere. Between 1979 and 1981, M-mode echocardiograms were performed on surviving subjects who participated in the 16th biennial examination (hereafter referred to as the index examination). At this index examination, routine histories, physical examinations, and laboratory evaluations were obtained. Surveillance for development of cardiovascular disease included routine procurement of outside physician reports and hospital records. Every suspected cardiovascular event was reviewed by a committee of three physicians who examined all available evidence.

Definitions

High blood pressure was defined as elevated systolic (≥160 mm Hg) or diastolic (≥95 mm Hg) blood pressure on each of
two measurements by physicians. Subjects were considered hypertensive if they had high blood pressure or were receiving drug treatment for hypertension at the index examination. The criteria for diabetes included a random nonfasting blood glucose level ≥11.11 mmol/L (200 mg/dL) and the use of insulin or an oral hypoglycemic agent. Valvular heart disease was considered present if a grade 3/6 or higher systolic murmur or any diastolic murmur was detected on physical examination. Coronary heart disease included angina pectoris, coronary insufficiency (unstable angina with documented ECG changes), or myocardial infarction. Criteria for coronary heart disease and congestive heart failure have been described previously.15

Subjects were excluded from this study for either of the following conditions: (1) a history of atrial fibrillation at or before the index examination or (2) a technically inadequate or unavailable echocardiogram at the index examination. Subjects with echocardiographically determined mitral stenosis were excluded from eligibility in accordance with other investigations of nonrheumatic atrial fibrillation.7,8

The initial assessment of atrial fibrillation was made by the examining physician on interpretation of a 12-lead ECG obtained at each routine Framingham Heart Study examination or by a review committee in the case of ECGs obtained from hospitalizations or office visits to outside physicians. All tracings were subsequently reviewed and verified by a cardiologist (D.L. or E.J.B.).

Echocardiographic Methods

Standard M-mode echocardiograms were routinely performed at the index examination. A 2.25-MHz, 1.25-cm-diameter, unfocused Aerotech transducer (KB Aerotech, Lewiston, Pa) and a Hoffrel 201 ultrasound receiver (Hoffrel Instruments, Norwalk, Conn) interfaced with a Honeywell 1856 strip chart recorder (Honeywell, Minneapolis, Minn) were used.

Left atrial size was determined in accordance with American Society of Echocardiography recommendations using a leading edge–to-leading edge convention to measure the maximal distance between the posterior aortic root wall and the posterior left atrial wall at end systole.19 Left ventricular wall thicknesses and internal dimensions were measured according to the methods described by Devereux and Reichek.17 (Penn convention). The modified cubed formula, which uses end-diastolic annular measurement, was determined in accordance with the Penn convention, was used to calculate left ventricular mass.15 Left ventricular mass (in grams) is equal to 1.04 [(left ventricular end-diastolic dimension plus septal wall thickness plus left ventricular posterior wall thickness) minus (left ventricular end-diastolic dimension)] 13.6. Left ventricular mass was standardized for body size by dividing left ventricular mass by height in millimeters.18

Mitral annular calcification was defined as the presence of a cluster of dense high-intensity echoes between the posterior left ventricular wall and the posterior mitral leaflet.19 Percent left ventricular fractional shortening was defined as 100 times the difference between the end-diastolic and end-systolic left ventricular internal dimensions divided by the end-diastolic left ventricular internal dimension. Mitral stenosis was assessed on the basis of decreased diastolic E-F closing slope, decreased mitral leaflet excursion, thickened mitral leaflets, and anterior motion of the posterior mitral leaflet.

Statistical Analysis

Cox proportional hazards regression models20 using the SAS procedure PHREG21 were used to study the relation between echocardiographic variables and the incidence of atrial fibrillation. In this model, subjects contributed to the follow-up until they (1) developed atrial fibrillation, (2) last attended a routine biennial examination, or (3) died of any cause during the designated follow-up interval. All regression models were stratified by age and sex. Echocardiographic variables evaluated were left atrial size, left ventricular internal dimensions (end-diastolic and end-systolic), ventricular septal and left ventricular posterior wall thicknesses, left ventricular mass/height, left ventricular fractional shortening, and mitral annular calcification. Both age- and sex-adjusted and age-, sex-, and clinical covariate–adjusted analyses were used to evaluate the impact of each echocardiographic variable on the risk of atrial fibrillation. The clinical covariates included in the model were coronary heart disease, congestive heart failure, hypertension (elevated blood pressure or use of antihypertensive medication), valvular heart disease, and diabetes. These clinical covariates were chosen because of their potential relation to either atrial fibrillation risk or echocardiographic findings.

Multivariable (age-, sex-, and clinical covariate–adjusted) proportional-hazards forward stepwise analysis was used to determine which echocardiographic variables independently contributed to the prediction of atrial fibrillation risk. In this analysis, echocardiographic variables were assessed both one at a time and simultaneously. The criteria for entry into the model and removal from the model were significance levels ≤0.10 and ≥0.05, respectively. The variable “sum of (left ventricular) wall thickness” was created and used in the stepwise analysis because the ventricular septal wall thickness and left ventricular posterior wall thickness variables were highly correlated with each other (r = 0.88).

Hazard ratios (HR) and 95% confidence intervals (95% CI) for atrial fibrillation incidence were calculated from the proportional-hazards analyses. For continuous variables, increments ± 1 SD were chosen. A two-sided P value < .05 was required to fulfill statistical significance.

The echocardiographic variables that remained significantly related to atrial fibrillation risk in the stepwise analysis were evaluated subsequently by quartile in an age- and sex-adjusted proportional-hazards model. In a further analysis, subjects were stratified according to the presence of highest-risk–quartile values for the echocardiographic predictors identified in the stepwise model (fourth quartile for left atrial size and left ventricular wall thickness; first quartile for left ventricular fractional shortening). Cumulative atrial fibrillation incidence rates, calculated according to the presence of 0, 1, 2 or 3 or more highest-risk–quartile values, were derived from age-adjusted Kaplan-Meier analysis.

Results

Study Sample

Of the 2351 subjects evaluated at the index examination, 1924 subjects (82%) were eligible for analysis after exclusions were made for prevalent atrial fibrillation, unavailable or technically inadequate echocardiograms, and mitral stenosis (Table 1). The eligible subjects ranged in age from 59 to 90 years; 61% were women. Information on baseline clinical characteristics was complete in >99% (1911/1924) of eligible subjects. These baseline characteristics are provided in Table 2. Subjects who developed atrial fibrillation during follow-up were older and more commonly had clinically apparent coronary heart disease and valvular heart disease.

Among eligible subjects, availability of echocardiographic data was greatest for left atrial dimension (100%) but was lower for left ventricular internal dimensions and wall thicknesses (67% to 69%) and mitral annular calcification (56%). Echocardiographic features of study subjects according to incident atrial fibrillation status are presented in Table 3.
Incidence of Atrial Fibrillation

There were 154 incident cases of atrial fibrillation during a total follow-up of 14,006 person-years. The incidence rates per 1000 person-years for subjects <70 years, 70 to 79 years, and ≥80 years old were 6.2, 13.0, and 34.1, respectively. Incidence rates rose sharply with age in both sexes and were higher in men than women across all age groups.

Analysis of Echocardiographic Variables

The results of the age- and sex-adjusted proportional-hazards regression analyses are summarized in Table 4. In the analyses, the relation of each echocardiographic variable to atrial fibrillation risk was statistically significant. After additional adjustment for coronary heart disease, valvular heart disease, hypertension, diabetes, and congestive heart failure, each echocardiographic variable remained significantly associated with risk of atrial fibrillation, with the exception of left ventricular end-diastolic dimension (Table 4).

The findings from the multivariable stepwise analysis are summarized in Table 5. In this analysis, left atrial dimension (HR per 5-mm increment, 1.39; P = .001), sum of left ventricular wall thickness (defined as septal wall thickness plus posterior wall thickness) (HR per 4-mm increment, 1.28; P = .03), and left ventricular fractional shortening (HR per 5% decrement, 1.34; P = .007) each maintained a statistically significant relation to atrial fibrillation risk when considered simultaneously.

The contribution of mitral annular calcification to the prediction of atrial fibrillation risk was analyzed separately because of the smaller number of subjects with mitral annular calcification data available. In a proportional-hazards model that adjusted for left atrial size, sum of left ventricular wall thickness, and left ventricular fractional shortening in addition to the clinical covariates (n = 843), mitral annular calcification remained marginally related to risk of atrial fibrillation (HR, 1.72; 95% CI, 0.93 to 3.18; P = .08).

Additional Analyses

The age- and sex-adjusted HRs according to quartiles of left atrial dimension, left ventricular fractional shortening, and left ventricular wall thickness (using the first quartile of the left atrial size and left ventricular wall thickness and the fourth quartile of left ventricular fractional shortening as the reference groups) are presented in Fig 1. For each variable, risk progressively increased as a function of successive quartiles. The HRs for the highest-risk quartiles of left atrial dimension, left ventricular fractional shortening, and left ventricular wall thickness were 2.72 (95% CI, 1.59 to 4.67), 2.50 (95% CI, 1.31 to 4.75), and 3.21 (95% CI, 1.43 to 7.21), respectively.

Cumulative atrial fibrillation incidence rates, derived from age-adjusted Kaplan-Meier analysis according to the presence and number of highest-risk-quartile echocardiographic values, are provided in Fig 2. Atrial fibrillation risk increased as a function of the number of highest-risk-quartile predictors present. At the completion of 8 years of follow-up, the cumulative incidence rates in the presence of one and two or more highest-risk-quartile values, respectively, were 7.3% and 17.0% compared with 3.7% when none was present.

Discussion

Echocardiographic Predictors

After adjustment for multiple potential confounders, three echocardiographic predictors of nonrheumatic
atrial fibrillation was common when the left atrial diameter exceeded 40 mm but rare when it was <40 mm. By demonstrating a stepwise increase in left atrial size from sinus rhythm to transient atrial fibrillation to chronic atrial fibrillation, these investigators suggested that atrial fibrillation was secondary to left atrial enlargement. In a further study by Takahashi et al.11 of 164

### TABLE 4. Adjusted Hazard Ratios for Risk of Atrial Fibrillation According to Individual Echocardiographic Variables

<table>
<thead>
<tr>
<th>Echocardiographic Variable</th>
<th>Variable Increment</th>
<th>Age and Sex Adjusted</th>
<th>Age, Sex, and RF Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left atrial dimension</td>
<td>5 mm</td>
<td>1.42 (1.24-1.64)§</td>
<td>1.31 (1.14-1.52)‡</td>
</tr>
<tr>
<td>Left ventricular end-diastolic dimension</td>
<td>5 mm</td>
<td>1.24 (1.03-1.48)*</td>
<td>1.13 (0.94-1.36)</td>
</tr>
<tr>
<td>Left ventricular end-systolic dimension</td>
<td>5 mm</td>
<td>1.40 (1.16-1.69)‡</td>
<td>1.29 (1.05-1.59)*</td>
</tr>
<tr>
<td>Ventricular septal wall thickness</td>
<td>2 mm</td>
<td>1.40 (1.20-1.62)§</td>
<td>1.34 (1.14-1.57)‡</td>
</tr>
<tr>
<td>Left ventricular posterior wall thickness</td>
<td>2 mm</td>
<td>1.56 (1.28-1.90)§</td>
<td>1.45 (1.17-1.79)†</td>
</tr>
<tr>
<td>Left ventricular mass/height</td>
<td>40 g/m</td>
<td>1.45 (1.25-1.69)§</td>
<td>1.34 (1.14-1.57)‡</td>
</tr>
<tr>
<td>Fractional shortening</td>
<td>&lt;5%</td>
<td>1.39 (1.14-1.69)†</td>
<td>1.33 (1.08-1.67)*</td>
</tr>
<tr>
<td>Mitral annular calcification</td>
<td>yes/no</td>
<td>1.92 (1.18-3.12)*</td>
<td>1.69 (1.02-2.80)*</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; RF, clinical risk factors (hypertension, coronary heart disease, congestive heart failure, valvular heart disease, and diabetes).

*P<.05; †P<.005; §P<.0005; ¶P<.0001.

### TABLE 5. Results of Multivariable Stepwise Analysis

<table>
<thead>
<tr>
<th>Echocardiographic Variable</th>
<th>Variable Increment</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left atrial dimension, mm</td>
<td>5</td>
<td>1.39 (1.14-1.68)</td>
<td>.001</td>
</tr>
<tr>
<td>Fractional shortening, %</td>
<td>&lt;5</td>
<td>1.34 (1.08-1.66)</td>
<td>.007</td>
</tr>
<tr>
<td>Sum of wall thickness, mm</td>
<td>4</td>
<td>1.28 (1.03-1.60)</td>
<td>.028</td>
</tr>
</tbody>
</table>

CI indicates confidence interval. Model is adjusted for age, sex, coronary heart disease, valvular heart disease, congestive heart failure, diabetes, and hypertension.

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Fig 1. Bar graph showing hazard ratios according to quartile of echocardiographic predictors. The hazard ratios, generated from Cox proportional-hazards analysis, were age stratified and sex adjusted. The first quartile is the reference group for left atrial size and sum of left ventricular (LV) wall thicknesses. The fourth quartile is the reference group for LV fractional shortening. Quartile parameters for each echocardiographic predictor are presented below.

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Quartile</th>
<th>Quartile</th>
<th>Quartile</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Left atrial dimension, mm</td>
<td>≤35</td>
<td>36-39</td>
<td>40-43</td>
</tr>
<tr>
<td>LV fractional shortening, %</td>
<td>≤35</td>
<td>36-38</td>
<td>39-41</td>
</tr>
<tr>
<td>Sum of LV wall thicknesses, mm</td>
<td>≤15</td>
<td>16-17</td>
<td>18-19</td>
</tr>
</tbody>
</table>
subjects with and without hypertension, ischemic heart disease, or rheumatic heart disease and in a more recent study by Keren et al\textsuperscript{12} of 68 subjects with mitral stenosis and 34 subjects with structurally normal mitral valves, similar stepwise increases in left atrial dimension according to the presence of sinus rhythm, transient atrial fibrillation, and chronic atrial fibrillation were also observed.

More recently, a prospective study with limited follow-up (mean, 20 months) of a small cohort (n=20) with preexisting left atrial enlargement (\(\geq 45\) mm) did not demonstrate an increased susceptibility to atrial fibrillation.\textsuperscript{25} Although study design limited the ability of previous studies to provide definitive proof that left atrial enlargement precedes the development of atrial fibrillation, recent follow-up studies have provided evidence that left atrial size increases after the onset of atrial fibrillation.\textsuperscript{26,27}

The independent contributions of left ventricular wall thickness and left ventricular fractional shortening to risk of atrial fibrillation have not been documented previously. Although left atrial size was correlated with left ventricular wall thickness (\(r=.38\) to \(.40\)) and to a lesser extent with fractional shortening (\(r=-.10\)), both left ventricular wall thickness and fractional shortening remained predictive of atrial fibrillation risk when considered simultaneously with left atrial dimension. Increased left ventricular wall thickness and/or impaired fractional shortening frequently accompany clinical conditions that are associated with increased atrial fibrillation incidence, such as hypertrophic,\textsuperscript{28} infiltrative,\textsuperscript{29} and ischemic\textsuperscript{30} cardiomyopathies.

Among the 1292 subjects with echocardiographic data available for all three predictors, the presence of multiple highest-risk-quartile measurements resulted in additive risk for atrial fibrillation. Subjects with at least two highest-risk-quartile measurements for left atrial size, left ventricular wall thickness, and left ventricular fractional shortening (19% of the study sample) were at greatest risk of developing atrial fibrillation (17% cumulative incidence over a period of 8 years). Conversely, subjects without highest-risk-quartile measurements for any of the three echocardiographic predictors (45% of the study sample) were at lowest risk for atrial fibrillation incidence (3.7% cumulative incidence over the 8-year follow-up interval). Of all incident atrial fibrillation events, 76% (73/96) occurred in subjects with at least one highest-risk-quartile value.

**Mechanisms of Increased Risk**

Although incompletely understood, atrial fibrillation is widely believed to result from multiple microentrant circuits, which are influenced by atrial properties such as tissue mass, refractory periods, and conduction velocities.\textsuperscript{31} The mechanisms by which increased left atrial size, increased left ventricular wall thickness, and decreased left ventricular fractional shortening may promote the development of atrial fibrillation are speculative. In all likelihood, left atrial dilatation is associated with structural and functional atrial tissue alterations that facilitate the disturbed impulse propagation of atrial fibrillation.\textsuperscript{10,12} Through altered ventricular filling patterns and impaired left atrial emptying, both left ventricular hypertrophy and decreased left ventricular fractional shortening may also result in atrial changes that facilitate the development of atrial fibrillation.

Evidence that increased left atrial size, increased wall thicknesses, and decreased left ventricular fractional shortening precede the development of atrial fibrillation does not necessarily imply causality. Abnormalities of these features may simply be markers for unidentified factors that are causally related to the development of atrial fibrillation. For example, hypertension and/or ischemic heart disease play roles in the development of left atrial enlargement,\textsuperscript{32,33} increased left ventricular wall thicknesses,\textsuperscript{32,34} and decreased left ventricular systolic function.\textsuperscript{35,36} However, high blood pressure and ischemia may also be causally related to atrial fibrillation incidence. Nonetheless, in this study, the three echocardiographic precursors remained predictive of atrial fibrillation risk after a large array of clinical factors that included hypertension and coronary heart disease were controlled for.

**Strengths and Limitations**

This study was based on a large, closely followed, population-based sample. By design, selection bias in this study population was minimized through the elimination of clinical referral patterns. To further reduce bias, all echocardiograms were interpreted in the absence of clinical information. Additionally, a thorough consideration of numerous clinical factors allowed care-
ful control for potential confounders in the comprehensive multivariable regression analyses.

Several limitations of this investigation deserve consideration. First, the study population is largely white and elderly, thus limiting the generalizability of these findings to nonwhite or younger populations. Second, the incidence of transient atrial fibrillation may have been underestimated because of reliance on 12-lead ECGs for detection. Third, echocardiographic data were not uniformly available for each echocardiographic feature and may have limited the analyses of those variables that were less available. In particular, analysis of the role of mitral annular calcification, which was technically more difficult to ascertain than other variables, involved a smaller subset of subjects and hence had reduced statistical power. However, there was no evidence of a systematic difference between the groups with and without mitral annular calcification data; the atrial fibrillation incidence rates in the two groups were virtually identical. An additional limitation may arise from the use of M-mode echocardiography, which lacks the sensitivity of two-dimensional echocardiography with Doppler color flow for the detection of valvular heart disease as well as regional wall motion abnormalities. However, >90% of the M-mode images were obtained with two-dimensional guidance, which increases the quantitative reliability of M-mode echocardiography. Nonetheless, clinically significant mitral regurgitation, well known to be associated with left atrial enlargement, cannot be evaluated by M-mode and, in the present study, was assessed by clinical examination alone.

Clinical Implications

In this elderly, population-based cohort, subjects with increased left atrial size, increased left ventricular wall thicknesses, or decreased left ventricular fractional shortening were at significantly increased risk for the development of nonrheumatic atrial fibrillation. In addition to providing a quantitative assessment of risk, the present study clarifies the roles of several cardiac structural and functional characteristics in relation to susceptibility to atrial fibrillation. The identification of cardiac structural and functional precursors of atrial fibrillation may enhance our understanding of mechanisms responsible for this dysrhythmia.

Perhaps the best method for reducing the adverse complications associated with atrial fibrillation is through prevention of the development of atrial fibrillation itself. Recent studies suggest that increased risk of thromboembolism exists in subjects with atrial fibrillation who have left atrial dilatation37,38 or decreased left ventricular systolic function.38 As such, subjects at greatest risk for the development of nonrheumatic atrial fibrillation may be at greatest risk for thromboembolic complications. The commonality of risk factors both for the development of atrial fibrillation and its complications suggests a role for preventive strategies. However, delineation of such preventive measures and their utility await additional investigation.

References


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