Longitudinal Tracking of Left Atrial Diameter Over the Adult Life Course: Clinical Correlates in the Community

David D. McManus, MD; Vanessa Xanthakis, MS; Lisa M. Sullivan, PhD; Justin Zachariah, MD; Jayashri Aragam, MD; Martin G. Larson, ScD; Emelia J. Benjamin, MD, ScM; Ramachandran S. Vasan, MD

Background—Increased left atrial diameter (LAD) is associated with elevated risk of atrial fibrillation (AF) and cardiovascular disease. Information is limited regarding the short- or long-term correlates of LAD.

Methods and Results—We evaluated clinical correlates of LAD for a 16-year period in 4403 Framingham Study participants (mean age, 45 years; 52% women; median observations/participant=3) using multilevel modeling. We related age, sex, body mass index (BMI), systolic and diastolic blood pressure (BP), diabetes, and antihypertensive treatment to LAD. Sex-specific growth curves for LAD were estimated for individuals with low, intermediate, and high risk factor burden. We also related risk factors to changes in LAD during a 4-year period in 3365 participants. Age, male sex (3.83 mm compared to women), greater BMI, higher systolic BP (0.24 mm per 10 mm Hg increment), and antihypertensive treatment (0.54 mm) were associated positively with LAD (P<0.001). Men had a greater increase in LAD with BMI than women (2.02 versus 1.77 mm in women, per 5-unit increment), and individuals receiving antihypertensive treatment experienced a greater increase in LAD with age (0.95 versus 0.63 mm per 10-year age increment) when compared with those not receiving antihypertensive treatment. Overall, greater risk factor burden was positively associated with LAD. These risk factors were also associated positively with 4-year change in LAD (P<0.001).

Conclusions—Our longitudinal study of a large community-based sample identified higher BP and greater BMI as key modifiable correlates of LAD, suggesting that maintaining optimal levels of these risk factors through the life course may prevent atrial remodeling and AF. (Circulation. 2010;121:667-674.)

Key Words: left atrial diameter ▪ atrial enlargement ▪ serial measurements ▪ epidemiology ▪ multilevel modeling ▪ echocardiography

Atrial fibrillation (AF) is the most common sustained dysrhythmia, affecting more than 2 million people in the United States.1 Preventing AF is a priority given the high lifetime risk for developing the condition, the projected increase in population burden, and the substantial morbidity and mortality associated with the disease.2 Identification and characterization of intermediate phenotypes for AF may identify high-risk individuals in advance of disease onset.2,3

Clinical Perspective on p 674

Atrial remodeling, a process characterized by atrial structural and electrophysiological changes, plays a central role in AF initiation and maintenance.2 Increased LAD is an echocardiographic marker of atrial remodeling and has well-established associations with the incidence of AF, heart failure, stroke, and all-cause mortality.3–7 LA enlargement is often seen in association with left ventricular dysfunction and valvular heart disease and in these settings reflects chronic LA volume or pressure overload.6,8 Whereas many risk factors have been identified for increased LAD and for AF in cross-sectional studies, little is known about the clinical determinants of longitudinal changes in LAD through the adult life course.9

We hypothesized that clinical factors associated with greater LAD in cross-sectional studies and with incident AF prospectively (eg, age, sex, adiposity, systolic and diastolic blood pressure [BP], diabetes, treatment with antihypertensive medication)9–15 are also key correlates of long-term tracking of LAD during adulthood. We also postulated that cumulative risk factor burden would influence LAD at both baseline and its tracking across the adult life course. We tested these hypotheses by evaluating the clinical correlates...
correlates and short-term change (4 years) in LAD.

Methods

Study Sample

The study sample comprised 4403 Framingham Offspring Study participants. The design of the Framingham Offspring Study was described previously. In brief, participants are evaluated at the Heart Study approximately every 4 to 8 years. Each Heart Study visit includes a physician-administered medical history and physical examination, anthropometry, and laboratory evaluation of standard risk factors.

For the present investigation, we focused on attendees at examination cycles 2 (1979–1982), 4 (1987–1990), 5 (1991–1995), and 6 (1996–1998), at which the participants underwent routine echocardiography (see below). Echocardiographic observations were excluded from this analysis for the following reasons: missing LAD (3706 observations); age <25 or ≥75 years at any of the eligible examinations (303 observations); and prevalent AF (195 observations), myocardial infarction or heart failure (437 observations), or valvular disease (174 observations) at these examinations. All of the observations with missing covariates (84 observations) were also excluded, leaving 13 293 echocardiographic observations. Due to the nature of statistical modeling, although 3706 echocardiographic observations were missing, only 30 unique participants with missing LAD at each of the eligible examinations were excluded from the overall analysis. Participants were considered to have valvular heart disease if either a grade 3/6 or higher systolic murmur or any diastolic murmur was auscultated by the Heart Study physician. Criteria used for defining myocardial infarction and heart failure have been described previously. AF was determined from 12-lead electrocardiograms obtained at each examination and by reviewing electrocardiograms obtained from hospitalization records or physician office visits. Study participants provided written informed consent, and the study protocol was approved by the institutional review board at the Boston University Medical Center.

Echocardiographic Examinations

Each participant completed a maximum of 4 sets of echocardiographic measurements at examination cycles 2, 4, 5, and 6, yielding 13 293 observations (Figure 1) for the longitudinal analyses (median number of observations per participant = 3). Although echocardiographic equipment differed across examinations, all of the echocardiograms were performed by experienced technicians and evaluated by trained technicians or cardiologists using a standardized protocol. LAD was determined from M-mode echocardiograms in accordance with the American Society of Echocardiography guidelines using a leading edge–to–leading edge technique, measuring the maximal distance between the posterior aortic root wall and the posterior LA wall at end systole. Although data on the longitudinal reproducibility of LAD measurements using different echocardiographic equipment are lacking, excellent inter- and intraobserver reproducibility for M-mode measurements of LAD have been reported in cross-sectional studies using these methods, including at the Framingham Heart Study.

Analyses of short-term LAD change focused on 3365 participants who attended 2 consecutive Heart Study examinations, at which echocardiography was performed (Figure 1). Whereas our longitudinal analyses focused on absolute LAD as the outcome variable, our short-term analyses examined change in LAD (regression coefficients for risk factors in the 2 sets of analyses are not directly comparable). Data from pairs of examination cycles (4, 5) and (5, 6) were pooled to maximize the number of observations available for short-term analyses (5933 echocardiographic observations).

Statistical Analyses

Multilevel Modeling

Multilevel statistical modeling allows for the analysis of data that vary both within and between participants in a longitudinal study with serial multiple observations on individuals (Figure 1). This approach has the advantage of accommodating study participants with missing data at 1 or more examinations, thereby increasing the number of observations available for analyses and enhancing statistical power to detect key correlates of LAD. The method also allows for variable time intervals between serial examinations.

Growth Curves Relating LAD to Clinical Covariates

Using a multilevel statistical model adjusted for relatedness of individuals (SAS PROC MIXED with a “random statement,” using an unstructured correlation matrix; SAS, Cary, NC), we related LAD (dependent variable) to the following risk factors (independent variables): age, sex, adiposity (BMI), systolic BP, diastolic BP, use of antihypertensive medications, and diabetes. These clinical variables were chosen a priori on the basis of their cross-sectional associations with LA enlargement and AF, and their association with LAD was examined using a direct entry model-building approach. Values for covariates were obtained from examinations corresponding to LAD assessment. Data are presented as increment in LAD per unit increment in continuous covariates.

The association of baseline LAD with follow-up LAD was determined by relating tertiles of baseline LAD to mean LAD change in 4 years. The examination cycle was included as a variable in our analyses to adjust for differences in LAD related to changes in echocardiographic instrumentation. Nonlinear effects of age also were examined, but they were not statistically significant. Interaction terms for each covariate with age and sex were investigated using multivariable models.

Growth Curves for LAD Based on Risk Factor Burden

To graphically illustrate the effect of age on LAD, 3 groups (low, intermediate, and high risk factor burden) were created for men and women on the basis of their risk factor profile, and growth curves for LAD were generated adjusting for other variables in our random effects model (Figures 2A and B). Because BP and BMI emerged as the key correlates, levels of these risk factors were used to define the 3 groups: women and men with a BMI of 25 kg/m² with normal BP (defined as having a BP of 113/73, median BP for normotensive participants) and not receiving antihypertensive medications were considered to have a low risk factor burden; individuals with a BMI of 27.5 kg/m² and prehypertension (defined as having a BP of 133/86, median BP for prehypertensive participants) and not receiving antihypertensive medications were considered to have an intermediate risk factor burden; those with a BMI of 30 kg/m² and hypertension (defined as having a BP of 146/91, median BP for hypertensive participants) were categorized as having a high risk factor burden. Thus, the median BP values used for plotting growth curves were determined from participants with BP values falling in normal, prehypertensive, or hypertensive ranges.
Analyses of Short-Term Changes in LAD
Generalized estimating equations were used to evaluate the clinical correlates of changes in LAD in the short term (4-year mean follow-up). Multivariable models adjusted for the same set of covariates used in the long-term analyses. Interaction terms examined in long-term analyses were also examined in short-term analyses.

A 2-sided $P$ of $<0.05$ indicated statistical significance. The authors had full access to the data and take responsibility for its integrity. All of the authors have read the article as written and agreed with submission in its current form.

Results
The baseline clinical and echocardiographic characteristics of the study samples are shown in Table 1.

Clinical Correlates of Long-Term LAD Tracking
Age, male sex, BMI, systolic BP, and use of antihypertensive medications were positively related to LAD, whereas diastolic BP was inversely related (Table 2). When pulse pressure was substituted for systolic and diastolic BP, LAD was positively related to pulse pressure (0.48 mm increase per 20 mm Hg increment in pulse pressure, $P<0.0001$). Statistically significant interactions were observed for sex and BMI, for age and antihypertensive medication use, and for sex and diastolic BP. Higher BMI was associated with a greater increment in LAD in men compared with women ($P=0.009$). Lower diastolic BP was associated with a greater increment in LAD in men.
compared with women ($P=0.009$). A greater increment in LAD was noted with advancing age in participants receiving antihypertensive medications compared with those not receiving antihypertensive treatment ($P=0.003$).

Table 2. Clinical Correlates of Longitudinal Tracking of LA Size for a 16-y Period

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Effect on LA Size, mm</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex*</td>
<td>3.83</td>
<td>3.62–4.04</td>
</tr>
<tr>
<td>Age (10-y increase; use of antihypertensive medications)</td>
<td>0.95</td>
<td>0.74–1.15</td>
</tr>
<tr>
<td>Age (10-y increase; no use of antihypertensive medications)</td>
<td>0.63</td>
<td>0.55–0.72</td>
</tr>
<tr>
<td>BMI (5-U increase, men)</td>
<td>2.02</td>
<td>1.87–2.18</td>
</tr>
<tr>
<td>BMI (5-U increase, women)</td>
<td>1.77</td>
<td>1.66–1.88</td>
</tr>
<tr>
<td>Systolic BP (10 mm Hg increase)</td>
<td>0.24</td>
<td>0.18–0.30</td>
</tr>
<tr>
<td>Diastolic BP (10 mm Hg increase, men)</td>
<td>$-0.39$</td>
<td>$-0.52$ to $-0.26$</td>
</tr>
<tr>
<td>Diastolic BP (10 mm Hg increase, women)</td>
<td>$-0.19$</td>
<td>$-0.31$ to $-0.06$</td>
</tr>
<tr>
<td>Use of antihypertensive medications**</td>
<td>0.54</td>
<td>0.29–0.78</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; BP, blood pressure; LA, left atrial. Table shows the change in LA size per increment of the predictor variable as indicated. There was a significant interaction of age and use of antihypertensive medications, diastolic BP and sex, as well as BMI and sex. Therefore, the effects of age, diastolic BP, and BMI are provided in the appropriate subgroups (men and women, and use and nonuse of antihypertensive medications).

*The effect of male sex (as compared with female sex) is for participants with an age of 51 years (mean age of all participants at all examinations), diastolic BP of 80 mm Hg, and BMI of 25 kg/m² due to the inclusion of sex in significant interaction terms.

**The effect of use of antihypertensive medications is for participants aged 51 years.

Baseline LAD was inversely related to short-term change in LAD. Compared with participants in the highest tertile of baseline LAD (LAD $>39.5$ mm), participants in the second tertile (34.5 mm $\leq$ LAD $\leq 39.5$ mm) and lowest tertile (LAD $<34.5$ mm) experienced a 1.9-mm and 4.5-mm greater change in mean LAD over time, respectively ($P<0.001$ for both).

We did not observe a significant association of diabetes with long-term tracking of LAD. Given the strong association between increased BMI and diabetes, we suspected that inclusion of BMI in our long-term models confounded the association between diabetes and LAD. After exclusion of BMI as a covariate in the models, multivariable modeling allowed for detection of a statistically significant positive association of diabetes with LAD ($P<0.0001$). When analyses were repeated incorporating body surface area instead of BMI as a measure of body size in multivariable models, we observed risk factor associations with LAD that were consistent with those noted for models with BMI (data not shown).

Impact of Risk Factor Burden on LAD in Adulthood

When compared with participants with intermediate levels of BP and BMI, participants with higher BP and BMI had a larger baseline LAD and a greater LAD increase in the 16-year follow-up period (Figure 2). Individuals with an optimal level of BP and BMI had smaller LAD at baseline and experienced lesser increments in LAD on follow-up relative to the other 2 groups. Figure 2 illustrates a stepwise increase in LAD at baseline and on follow-up with increasing BP and BMI (ie, the change in LAD from low to intermediate...
Changes in LAD are associated with increased risk of AF, including measures of body size. These observations are consistent with some investigations that reported sex-related differences in LA volumes. Absolute risk of AF is higher in men compared with women, and we speculate that this may be related in part to availability of a greater amount of atrial myocardium that serves as a substrate for the dysrhythmia. Our findings differ, however, from some previous cross-sectional studies that have reported sex-related differences in LAD.}

### Discussion

#### Clinical Correlates of Short-Term Changes in LAD

Analyses identified male sex, age, BMI, systolic BP, and use of antihypertensive medications as key clinical correlates of short-term changes in LAD (Table 3). In addition, baseline LAD was inversely associated with short-term changes in LAD. The statistical interaction term (male*diabetes) was associated positively with LAD change, indicating that men with diabetes had greater changes in LAD compared with men without diabetes (\(\beta = 3.29, p = 0.001\)).

#### Comparison with Published Literature

**Relation of Age to LAD**

Autopsy, echocardiographic, and radiographic studies have shown that advancing age is associated with increasing LAD. These changes have been attributed in part to age-associated alterations in myocardial (atrial) tissue composition. Recent analyses using volumetric atrial data suggest that atrial enlargement may not be part of the “normal” aging process per se but may be the consequence of a greater burden of risk factors that accompanies aging. Our data suggest that age is a significant correlate of short-term and long-term LAD even in individuals with a low risk factor burden (Figure 2, panels A and B); however, risk factor burden strongly influenced LAD at baseline and during follow-up.

**Relation of Sex to LAD**

Men in our sample had higher LAD at baseline and on short- and long-term follow-up after accounting for several covariates, including measures of body size. These observations are consistent with some investigations that reported sex-related differences in LA volumes. Absolute risk of AF is higher in men compared with women, and we speculate that this may be related in part to availability of a greater amount of atrial myocardium that serves as a substrate for the dysrhythmia.

**Relation of Adiposity (BMI) to LAD**

Several cross-sectional studies have demonstrated that obesity and greater BMI are important correlates of larger LAD. A greater degree of LA enlargement over time with higher BMI levels and with lower diastolic BP (as compared with women). Participants receiving antihypertensive medications also had a greater increase in LAD with increasing age compared with those participants not receiving antihypertensive treatment. Higher BMI and BP during midlife were associated with greater LAD over time. Of note, we did not find an independent association of diabetes with long-term tracking of LAD in the present investigation, although an association of diabetes with change in LAD was observed in men in the short-term analyses. The inverse relation of baseline measurements to LAD on follow-up in short-term analyses likely reflects in part the phenomenon of “regression to the mean,” which is well known in longitudinal epidemiological investigations with serial measurements of select variables.
Higher BMI is also an important predictor of AF incidence in longitudinal studies. In the present study, we confirm the cross-sectional association noted above using a longitudinal design. The mechanisms by which increased BMI promotes LA enlargement may relate to hemodynamic changes (including increased intravascular volume and cardiac output, and increased stroke volume), in addition to metabolic changes (including insulin resistance). We noted a modest sex-related difference in the relations of BMI and LAD on longitudinal analyses, with a steeper slope noted in men. These observations are consistent with a previous cross-sectional study from our group that noted that an SD increment in BMI resulted in a 10% greater increment in LAD in men (compared with women). Overall, these findings are also consistent with sex-related differences in cardiac remodeling responses to volume-overload states. Men experience greater left ventricular dilation in response to hemodynamic changes, and it is conceivable that this response pattern extends to LAD.

Relation of Systolic BP and Pulse Pressure to LAD
Systolic BP and pulse pressure have been shown to be associated with greater LAD in a previous cross-sectional report from the Framingham Study and with greater risk of AF prospectively. Increased cardiac pulsatile load, as indicated by a higher pulse pressure, promotes LA enlargement and is a key mediator of increased AF risk, especially in older adults. Our analyses are consistent with these observations. Of note, we noticed a stronger association of lower diastolic BP with LAD in men (compared with women) in our longitudinal analyses. Additional studies are warranted to confirm this latter finding, which may suggest a greater impact of pulsatile hemodynamics on LAD in men.

Relation of Diabetes to LAD
Although we observed a statistically significant interaction between diabetes and sex in our short-term analysis, diabetes was not independently associated with long-term tracking of LAD. Although our study conflicts with prior work showing an association between diabetes and increased LAD, it is noteworthy that the association between diabetes and LAD in that study was markedly attenuated by adjustment for BMI and rendered statistically nonsignificant after adjustment for history of AF. Because higher BMI is a strong risk factor for diabetes and diabetes may be along the causal pathway from BMI to greater LAD, adjustment for BMI in our long-term analyses may result in an underestimation of the potential contribution of diabetes to LAD.

Strengths and Limitations
The strengths of the present investigation include the use of multilevel modeling in a large community-based sample with multiple serial echocardiographic observations and a comprehensive evaluation of both short-term change in and long-term tracking of LAD.

Our study has important limitations. First, the observational nature of our study precludes causal inferences. Second, although M–mode-based measurement protocols for LAD were consistent during the long study period, changes in echocardiographic instrumentation raise issues of comparability across examinations. Any differences in LAD across examinations would likely have resulted in random misclassification, however, and would bias toward the null hypothesis of no association of LAD with clinical covariates studied. In addition, we adjusted for “examination cycle” in our analyses to account for changes in instrumentation. Third, the anteroposterior LA dimension provided by M-mode and used for the determination of LAD in our analyses may not reflect true atrial size. Although the LA generally enlarges in a spherical fashion, symmetrical enlargement does not always occur, and thus volumetric assessment of LA size is a more accurate measure of atrial size. M-mode–based LA assessment is, however, a well-studied and valid measure of LA size, and we were limited by the availability of only M-mode data in the Framingham Study at the earlier examination cycles. Fourth, we excluded individuals with valve disease defined on the basis of physical examination, which may not be as sensitive as Doppler echocardiographic assessment (the latter was not available at earlier examinations). It is likely that some individuals in our sample had valve disease, which could increase LAD. Fifth, 30 participants were excluded on the basis of missing LAD measurements. These participants were older and more likely to be hypertensive (higher systolic BP level and use of antihypertensive medications) than participants included in our study sample. It is possible that the exclusion of these participants influenced our findings. Sixth, participants in the Framingham Offspring cohort are middle aged to elderly and largely white. The generalizability of our findings to other age or racial groups is unknown.

Conclusions
Given the increasing prevalence of AF in the United States and worldwide, it is important to identify and characterize important precursors, such as increased LAD. Our longitudinal investigation of a large community-based sample identified higher BP and BMI as key risk factors for short- and long-term changes in LAD. Indeed, individuals with a higher risk factor burden had greater LAD equivalent to 20 years of aging, relative to those with optimal risk factors. These data, although observational, are consistent with the notion that maintenance of optimal levels of BP and BMI during the life course may be critical for preventing increases in LA size that accompany the aging process and may aid the prevention of AF.

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Disclosures
None.
None.

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13. McManus et al Correlates of Long-Term LA Diameter 673

**CLINICAL PERSPECTIVE**

Preventing atrial fibrillation (AF) is a public health priority in light of the high lifetime risk for this condition, the projected increase in population burden, and the substantial morbidity and mortality associated with the disease. Increased left atrial diameter (LAD), a marker of left atrial remodeling, is associated with elevated risk of AF (new onset and recurrent). This association has led to the hypothesis that increased LAD may represent an intermediate phenotype in the progression from risk factors to AF, especially in older individuals. Information is limited, however, on short- and long-term clinical correlates of LAD across the adult life course. In this investigation of a large, community-based sample, we used multilevel modeling to evaluate correlates of LAD during a 16-year period and also related these risk factors to short-term change in LAD (during a 4-year period). We identified higher blood pressure and greater body mass index as key correlates of both short-term LAD change and long-term tracking of LAD. Using sex-specific growth curves for LAD, we also observed that LAD at baseline and over time was positively associated with greater risk factor burden. The results of our study suggest that maintenance of optimal levels of blood pressure and body mass during adulthood may be critical for preventing atrial remodeling and AF.
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