Left Atrial Systolic Force and Cardiovascular Outcome

The Strong Heart Study

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Background: The force needed to fill the left ventricle (LV) in late diastole (left atrial systolic force [LASF]) is abnormal in diseased hearts. The goal of this study was to determine whether LASF adds to prognostic prediction of other markers of preclinical cardiovascular disease in a population with a high prevalence of hypertension and diabetes.

Methods: Doppler echocardiography was performed on 2808 participants of the Strong Heart Study (age 59.3 ± 8.0 years, 62.5% women, 43.0% hypertensive, 46.7% diabetic, and 54.1% obese) without valvular abnormalities or previous cardiovascular events. The LASF was estimated from mitral orifice area and mitral peak A velocity.

Results: The LASF was correlated with older age, higher BP, body mass index, creatinine, serum glucose, insulin levels, and heart rate. After controlling for clinical covariates, LASF was independently associated with higher LV dimensions, LV mass, stroke volume, and cardiac output (all P < .01). In Cox regression analysis, greater LASF was associated with a higher rate of CV events (HR = 1.033, 95% CI = 1.005 to 1.061; P = .021), independently of demographic characteristics, risk factors, LV geometry, and transmitral diastolic pattern.

Conclusions: In a population-based sample of middle-aged and elderly adults with a high prevalence of hypertension and diabetes and without prevalent cardiovascular disease, LASF was associated with geometric changes of the heart and with increased rate of combined fatal and nonfatal cardiovascular events. Am J Hypertens 2005; 18:1570–1576 © 2005 American Journal of Hypertension, Ltd.

Key Words: Echocardiography, atrial function, diastole, and prognosis.

In clinical practice, left ventricular (LV) diastolic properties are commonly estimated by the ratio between Doppler echocardiographic early and late (or atrial) peak flow velocities (E/A ratio).1 The E/A ratio is most commonly used as a surrogate estimate of the balance between LV chamber relaxation and myocardial stiffness and is abnormal in a number of morbid conditions including myocardial infarction,2 hypertrophic cardiomyopathy,3 hypertensive LV hypertrophy,4 diabetes,5 and obesity.6 Recently E/A ratio has been described to predict CV events,7,8 but this finding does not indicate whether atrial activity is also prognostically relevant. In fact the E/A ratio only partially reflects the work that the left atrium performs to contribute to complete LV diastolic filling.9,10 Atrial contribution is especially important when reduced net early diastolic atrioventricular gradient does not allow efficient rapid filling, a condition related to prolonged active LV relaxation. In these conditions, atrial force is often increased. We have recently reported that in hypertensive patients without prevalent cardiovascular disease, enhanced LASF is associated with LV hypertrophy, increased cardiac output, and increased transmural

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flow, also occurring during rapid filling despite prolonged relaxation.\textsuperscript{14} Although predictive value of reduced left atrial contraction force in patients who have undergone cardioversion from atrial fibrillation has been reported,\textsuperscript{12} no data have been published concerning the prognostic relevance of left atrial force in population studies.

Accordingly, this study has been designed to test the hypothesis that in a population with a high prevalence of hypertension and diabetes, LASF extends understanding of diastolic physiology and adds prognostic information to the commonly used mitral E/A ratio.

**Methods**

**Study Population**

The Strong Heart Study is a longitudinal study designed to determine cardiovascular disease mortality and morbidity rates and prevalence of risk factors for cardiovascular disease in middle-aged to elderly American Indians. The study population consists of 13 tribes in Arizona, Oklahoma, and North and South Dakota. Details of recruitment and characteristics of the population have previously been described.\textsuperscript{13} For the purpose of the present study of 3501 participants in the second Strong Heart Study phase who underwent echocardiography, data from the 2808 participants who were without prevalent cardiovascular disease, valvular disease, or cardiac rhythm abnormalities at the time of the echocardiogram and had recordings suitable for measurements of LV dimension and mass were retrospectively analyzed. The data analyses included results from 1053 men and 1755 women (34% Arizona, 33% North and South Dakota, and 33% Oklahoma).

**Echocardiographic Methods**

As previously described in detail,\textsuperscript{14} echocardiograms were recorded in a partial left decubitus position using phased-array echocardiographs with M-mode, two-dimensional, and Doppler capabilities. A standardized protocol was followed under which needed images and Doppler flow patterns were recorded in 10 consecutive beats from appropriate acoustic windows, with participants holding their breath during recording.\textsuperscript{15} To relate better the measurements of LV diastolic transmitral flow velocity to volume flow, the pulsed Doppler sample volume was placed at the middle of the mitral annulus.\textsuperscript{16}

**Echocardiographic Measurements**

Measurements were obtained as previously reported\textsuperscript{14} using a computerized review station. The LV measurements were performed according to the American Society of Echocardiography recommendations on up to three cycles.\textsuperscript{17} When optimal M-mode beam orientation through the left ventricle could not be obtained, correctly oriented two-dimensional linear dimensions were measured.\textsuperscript{18} The leading edge of trans-mitral Doppler flow pattern was traced to derive peak of early (E) diastolic and atrial-phase (A) velocities, their ratio, deceleration time of E velocity, and atrial filling fraction.

**Calculation of Derived Variables**

Standard methods were used to calculate relative wall thickness\textsuperscript{19} and LV mass from either M-mode\textsuperscript{20} or two-dimensional\textsuperscript{21} measurements. Stroke volume was determined by an invasively validated Doppler method\textsuperscript{22} and used to calculate cardiac output. The LV mass was normalized for body height to the power of 2.7.\textsuperscript{23} Gender-specific partition values in men and women for LV mass/height\textsuperscript{2.7} (49.2 and 46.7 g/m\textsuperscript{2.7}) represent upper limits of normal gender-specific 95% confidence intervals in reference populations. End-diastolic volume was calculated by the Z derived method\textsuperscript{24} and was used with Doppler stroke volume to calculate ejection fraction.

**Assessment of LASF**

The LASF was assessed according to the following general principle: Force = mass × acceleration. According to a previously validated formula,\textsuperscript{10,25} mass was defined as the product of the density of the blood (ie, 1.06 g/cm\textsuperscript{3}) and the volume of blood passing through the mitral orifice during atrial contraction.

Mitral orifice area (MOA) was calculated by continuity equation with Doppler stroke volume at the aortic valve divided by time velocity integral at the mitral annulus, under the assumption that in the presence of nonregurgitant mitral valve, the transaortic ejected blood volume equals the volume passing through the mitral valve during diastole.\textsuperscript{26} The pressure half-time method was not used because it is influenced by LV diastolic properties.\textsuperscript{27}

Therefore the volume of blood (v) through the mitral orifice was defined as follows:

\[
v = \text{MOA} \times \left[ \frac{(\text{peak A} \times \text{time to peak A})}{2} \right]
\]

Acceleration of blood during atrial systole (a) was obtained as:

\[
a = \text{peak A}/\text{time to peak A}
\]

Replacing these variables in the general equation of force:

\[
\text{LASF} = 1.06 \times \text{MOA} \times \left( \frac{\text{peak A} \times \text{time to peak A}}{2} \right) \times \left( \frac{\text{peak A}/\text{time to peak A}}{2} \right)
\]

and therefore

\[
\text{LASF} = 0.53 \times \text{MOA} \times (\text{peak A velocity})^2
\]

**Clinical Endpoints**

For analysis of cardiovascular events, observations began on the date of echocardiography (between 1993 and 1995), with ascertained events updated through January 2001. Deaths were identified from sources in each community and through annual follow-up of participants and were verified through death certificates and review of medical
records. Death was classified as cardiovascular if caused by myocardial infarction, stroke, sudden death from coronary heart disease (CHD), or congestive heart failure (CHF). Nonfatal events (nonfatal myocardial infarction or stroke, hospitalization for new CHF or new CHD identified by coronary angiography, percutaneous transluminal coronary angioplasty, coronary bypass, abnormal stress electrocardiography with abnormal imaging, or positive treadmill test for ischemia) were reviewed through the medical records by trained abstractors, as previously described. Records of outpatient visits were reviewed and abstracted for diagnostic procedures. To classify cardiovascular events, an independent panel of physicians who were unaware of the echocardiographic findings reviewed information obtained in the charts.

Statistical Analysis

Statistical analysis was performed using SPSS version 11.0.1 software (SPSS Inc., Chicago, IL) software. Data were expressed as mean ± 1 SD. Distribution of LASF was assessed by the Kolmogorov-Smirnov test. Partial correlation was used to evaluate independent association of LASF with cardiac geometry and function, after controlling for gender, age, heart rate, body mass index (BMI), presence of hypertension, antihypertensive treatment, presence of diabetes, and transmitral inflow pattern. Because the relationship between E/A ratio and cardiovascular morbidity and mortality is not linear but instead quadratic, categories of E/A for abnormal relaxation (ie, E/A < 0.6), normal filling (ie, 0.6 ≤ E/A ≤ 1.5), or restrictive physiology (E/A ≥ 1.5)7 were used in the multivariate analysis as indicator variables. Cox proportional hazards regression was used to determine the independent effect of LASF on incident cardiovascular events after adjusting for relevant covariates. A two-tailed P value < .05 indicated statistical significance.

Results

Gender-specific characteristics of the study population are shown in Table 1. The LASF distribution was assessed in a subgroup of 246 untreated normotensive, nondiabetic, normal weight participants of the study population. The distribution was normal with a mean value of 10.48 kdynes, and the 5th, 10th, 90th, and 95th percentiles of 4.15 kdynes, 5.90 kdynes, 14.33 kdynes, and 18.00 kdynes respectively.

Relationship Between LASF and Clinical Characteristics of Study Population

The LASF was similar in men and women (12.5 ± 4.7 kdynes v 12.2 ± 4.7 kdynes; P = NS) but was signifi-
Table 3.  Echocardiographic correlates of left atrial systolic force (LASE), controlling for confounders

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
<th>Partial correlation coefficient</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LASF</td>
<td>12.29 ± 4.68</td>
<td>—</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Left atrial diameter (cm)</td>
<td>3.50 ± 0.45</td>
<td>0.158</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LV diastolic diameter (cm)</td>
<td>4.93 ± 0.47</td>
<td>0.439</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LV mass/h^2.7 (g/m^2.7)</td>
<td>41.14 ± 10.18</td>
<td>0.248</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.35 ± 0.05</td>
<td>−0.253</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LV hypertrophy (%)</td>
<td></td>
<td>22.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Stroke volume (mL)</td>
<td>70.99 ± 15.9</td>
<td>0.549</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cardiac output (mL/min)</td>
<td>4714 ± 1130</td>
<td>0.335</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>70.87 ± 11.84</td>
<td>0.063</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Peak E velocity</td>
<td>57.9 ± 16.3</td>
<td>−0.002</td>
<td>NS</td>
</tr>
<tr>
<td>Peak A velocity</td>
<td>71.0 ± 16.0</td>
<td>0.750</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mitral E deceleration time (msec)</td>
<td>206.0 ± 67.8</td>
<td>−0.043</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

LV = left ventricular.
* P values corrected for age, gender, heart rate, body mass index, presence of hypertension, hypertensive treatment, presence of diabetes and E/A ratio class.
† LV hypertrophy defined as LV mass/height^2.7 > 49.2 g/m^2.7 for men and >46.7 g/m^2.7 for women.

Cardiovascular Events

During a follow-up of 60 months, 242 cardiovascular events were noted (8.6% of study population). In a Cox regression model, controlling for age and gender (Table 4), independent predictors of increased cardiovascular risk were the presence of hypertension (P = .005), diabetes (P = .001), cigarette smoking (P = .002), higher LV mass index (P = .041), presence of restrictive physiology (P = .025), and lower ejection fraction (P = .004). In addition to these covariates, greater LASF was another independent predictor of combined fatal and nonfatal CV events (P = .021). The independent predictive power of LASF did not change significantly when LA diameter was included in the Cox regression model (P = .029).

An alternative approach considering quintiles of LASF showed similar CV event rates in participants in the lowest three quintiles of LASF (7.7%, 7.4%, and 6.7% respectively (P = NS). In contrast, a significant increase in CV event rate was found in the highest quintiles (9.4% and 13.3% respectively, for both P < .05 compared with other

Table 4. Cox proportional hazards for cardiovascular events

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.040</td>
<td>1.023–1.058</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gender (women)</td>
<td>0.861</td>
<td>0.650–1.140</td>
<td>NS</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>1.548</td>
<td>1.177–2.035</td>
<td>.002</td>
</tr>
<tr>
<td>Presence of hypertension</td>
<td>1.329</td>
<td>1.185–1.492</td>
<td>.005</td>
</tr>
<tr>
<td>Presence of diabetes</td>
<td>2.213</td>
<td>1.661–2.950</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Left ventricular mass index</td>
<td>1.011</td>
<td>1.002–1.023</td>
<td>.041</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.025</td>
<td>0.004–0.176</td>
<td>.004</td>
</tr>
<tr>
<td>E/A class (abnormal relaxation versus normal)</td>
<td>1.132</td>
<td>0.822–1.560</td>
<td>NS</td>
</tr>
<tr>
<td>E/A class (restrictive physiology versus normal)</td>
<td>1.443</td>
<td>1.047–1.988</td>
<td>.025</td>
</tr>
<tr>
<td>LASF</td>
<td>1.033</td>
<td>1.005–1.061</td>
<td>.021</td>
</tr>
</tbody>
</table>

CI = confidence interval; LASF = left atrial systolic force. E/A class = see text (statistical analysis section) for explanation.
groups). A graphic representation of cardiovascular event-free rates in the study population is shown in Fig. 1.

**Discussion**

Usefulness of LA function in risk stratification has previously been described in selected groups of patients with diseased heart disease. However the prognostic importance of LASF in patients free of cardiovascular disease with a high prevalence of cardiovascular risk factors has not been reported. To our knowledge this is the first report on the independent prognostic value of atrial function in a population setting. We have recently reported, in an unselected population of hypertensive patients, that LASF depends on circulating volume and that high LASF consistently identifies hypertensive patients characterized by more marked obesity, high cardiac output, and increased LV mass index.11 In the present study we also report a significant, although mild, relationship between LASF and LA diameter. In our interpretation this positive relation is explained by the fact that when the early LA emptying rate is reduced, an increase in left atrial preload before contraction occurs to recruit Starling forces, with a consequent increase in atrial contribution to LV filling. However when the LA diameter is included in the Cox model, the significance of LASF in detecting incident cardiovascular event is not affected (P values 0.021 to 0.029), suggesting that the predictive power of LASF is independent of both ventricular and atrial geometry as well as of traditional markers of cardiac function. It is reasonable to suppose that similarly to what has been previously reported in patients with hypertrophic cardiomyopathy,28 atrial volume (which was not available in the Strong Heart Study database) would be more strongly related to LASF compared with LA diameter. Nonetheless we have recently reported that LA diameter might represent a reliable surrogate of LA volume in predicting incident cardiovascular events in Strong Heart Study participants without prevalent CV disease.29 In addition to LASF, other parameters can give information on LA function. Stefanadis et al validated use of LA kinetic energy in a number of pathologic conditions, and a model using a noninvasive method measuring LA maximum dP/dt, combining information from transmitral and pulmonary venous has been reported.30 The information needed to compute these alternative indices of atrial function were not included in the Strong Heart Study protocol and therefore could not be explored in the present report.

In diseased hearts, impairment of late passive LV compliance reduces the ability of the atrium to push blood into the high-pressure LV chamber, resulting in reduced left atrial force. In the present analysis, participants with cardiovascular disease at the time of echocardiography were not included in the study, thereby excluding participants with expected reduced LASF. This selection accounts for the mild insignificant increase in CV events that could be identified even in the lowest quintile of LASF.

Instead, when early LA emptying rate is reduced, left atrial preload and atrial contribution to LV filling increase. This explains why atrial force increases with age9 and in the presence of hypertension,11 where relaxation is prolonged.

In our Cox regression model we identified independent predictive values of both LASF and high E/A ratio (Table 4). There is an obvious negative relationship between LASF and E/A ratio, as the consequence of a direct relationship of LASF with peak A velocity, used in its computation. Prospectively however, both high LASF and high E/A ratio have similar negative prognostic relevance, which is independent of parameters of cardiac geometry and systolic function, a finding that cannot be influenced by mathematical tautology.

There are several limitations to this study that should be mentioned. First, the analysis was performed in American Indian populations, and whether these results can be generalized to other ethnic groups requires further study. A number of potential technical limitations might also be recognized. The mitral annulus orifice was computed from Doppler signal by a continuity equation, whereas two-dimensional biplane direct measurement might be preferred. Therefore a mean diastolic valve area was obtained, rather than the area at the time of atrial contraction. However, although the mitral annular area changes substantially during systole, its diastolic variation has been shown to be modest (approximately 11%).16 Furthermore the Doppler method eliminates the need for assumptions about geometric shape of the mitral annulus, which has also been shown to change during the cardiac cycle. Another limitation is that analysis of the LV diastolic filling pattern was performed placing the sample volume at the middle of the mitral annulus rather than at the level of the tips and therefore may reflect volume flow rather than transvalvular gradients that better approximate...

**FIG. 1.** Kaplan-Meier curve for cardiovascular event-free rates by classification of LASF. Study population is dichotomized using a partition value of 14.33 kdynes (90th percentile of the distribution in normal participants.)
interactions between chambers during diastole. However a stable measure of volume flow was important for our purposes because mitral annulus orifice was computed from Doppler signal by continuity equation. In addition pulmonary vein flow and left atrial volumes were not measured, and therefore neither the association between atrial volume and LASF nor the comparison between LASF and other validated indices of atrial function as LA kinetic energy and LA dP/dt could be performed.

In conclusion, in a population-based sample of middle-aged and elderly adults with high prevalence of diabetes and hypertension, and without prevalent cardiovascular event, LASF was found to be associated with structural changes of the heart and with increased rate of combined nonfatal and fatal cardiovascular events. The effect of LASF on incident CV disease is independent of prognostically validated markers of preclinical disease and evidence of restrictive filling (by high E/A ratio) at the level of the mitral annulus. In patients without prevalent cardiovascular disease, LASF may provide additional prognostic information that may also be very useful for understanding the physiopathology of evolving diastolic dysfunction in hypertensive patients. It should be noted that LASF does not exhaustively describe atrial function. Nonetheless it represents a noninvasive surrogate indicator of atrial contraction that can easily be obtained in the clinical setting from the mitral valve area and transmitral peak A velocity.

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References


