Mitral Ratio of Peak Early to Late Diastolic Filling Velocity as a Predictor of Mortality in Middle-Aged and Elderly Adults

The Strong Heart Study

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Background—With aging, left ventricular filling tends to decrease in early diastole, reducing the mitral ratio of peak early to late diastolic filling velocity (E/A). However, the prognostic significance of low or high E/A in older adults remains to be elucidated in population-based samples.

Methods and Results—Doppler echocardiograms were analyzed in 3008 American Indian participants in the second Strong Heart Study examination who had no more than mild mitral or aortic regurgitation. Participants were followed for a mean of 3 years after Doppler echocardiography to assess risks of all-cause and cardiac death associated with E/A <0.6 or >1.5; 2429 (81%) participants had normal E/A ratio, 490 (16%) had E/A <0.6, and 89 (3%) had E/A >1.5. All-cause mortality was higher with E/A <0.6 or E/A >1.5 (12% and 13% versus 6%), as was cardiac mortality (4.5% and 6.5% versus 1.6%; both P<0.001). Adjusting for age, sex, body mass index, systolic blood pressure, HDL and LDL cholesterol, smoking, hypertension, diabetes, coronary heart disease, left ventricular hypertrophy, and low ejection fraction (<40%), the relative risk of all-cause death with E/A >1.5 was 1.73 (95% CI, 0.99 to 3.03; P=0.05); the relative risk of cardiac death was 2.8 (95% CI, 1.19 to 6.75; P<0.05). E/A <0.6 was not independently associated with increased all-cause or cardiac mortality (P=0.19 and 0.31, respectively) after adjusting for covariates.

Conclusions—In a population-based sample of middle-aged and elderly adults, mitral E/A >1.5 at baseline Doppler echocardiography is associated with 2-fold increased all-cause and 3-fold increased cardiac mortality independent of covariates; mitral E/A <0.6 was also associated with 2-fold increased all-cause and cardiac mortality but not independent of covariates. (Circulation. 2002;105:1928-1933.)

Key Words: epidemiology ■ mortality ■ echocardiography ■ diastole ■ aging

With aging, left ventricular (LV) filling tends to decrease in early diastole, resulting in decreased peak early diastolic filling velocity with an increase in peak late (atrial) diastolic filling velocity.1,2 The age-related alterations in Doppler diastolic filling indexes are independent of LV mass, heart rate, contractility, and loading conditions.3 Of these measures, the ratio of peak early to late diastolic filling velocity (E/A ratio) is the simplest and most commonly used index to assess diastolic filling. Individuals with low E/A are considered to have impaired early diastolic relaxation; those with high E/A have a restrictive filling pattern.3,4 Although high E/A has been shown to be associated with worse outcome in dilated cardiomyopathy5 and acute myocardial infarction,6 this has not been established in population-based samples, and the prognostic significance of low E/A remains to be elucidated. Therefore, this study was undertaken to identify clinical correlates of the mitral E/A ratio in a population-based sample of middle-aged and elderly adults and to determine its impact on prognosis.

Methods
The Strong Heart Study (SHS) is a population-based cohort survey of cardiac risk factors and prevalent and incident cardiac disease in 13 American Indian communities: 3 in Arizona, 7 in Oklahoma, and 3 South and North Dakota. As previously described,7 tribal members 45 to 74 years of age were recruited for an initial examination in 1989 to 1992. The second SHS examination was conducted in 1993 to 1995 among survivors to assess change over time in body habitus, blood pressure (BP), and most other baseline measures and to add...
echocardiography; 3630 surviving enrollees from the first examination participated in the second examination (89% return rate). Diabetes was diagnosed by World Health Organization criteria. Hypercholesterolemia was defined as total cholesterol $>200$ mg/dL. Participants were classified as hypertensive if resting BP was $\geq 140$ mm Hg systolic and/or $90$ mm Hg diastolic or they took antihypertensive medications. Definite or possible coronary heart disease (CHD) was diagnosed on the basis of clinical and ECG evidence of CHD or myocardial infarction; participants were classified as having congestive heart failure (CHF) as previously described. For the present analysis, participants with $\geq 3$+ aortic or mitral regurgitation or heart rate $>100$ bpm were excluded.

Echocardiographic Methods

Imaging and Doppler echocardiograms were performed in 3501 participants (97%) in the second SHS examination with the use of previously described methods. Studies were performed with phased-array echocardiography with M-mode, 2-dimensional, and pulsed, continuous-wave, and color-flow Doppler capabilities. Correct orientation of planes for imaging and Doppler recordings was verified as previously described. LV internal dimension and septal and posterior wall thicknesses were measured at end-diastole and end-systole by American Society of Echocardiography recommendations. Color-flow Doppler recordings were used to search for aortic and mitral regurgitation, as previously described.

To facilitate relating measurements of LV diastolic transmitral blood flow velocity to volume flow, the pulsed Doppler sample volume was placed at the middle of the mitral annulus, the diameter of which varies relatively modestly during the cardiac cycle, as opposed to the leaflet tips, where the orifice shows substantial variation through the cardiac cycle. The leading edge of the transmitral Doppler flow pattern was traced to derive the peak of early diastolic and atrial phase LV filling ("E" and "A," respectively), their ratio, the deceleration time of early diastolic LV filling, and the atrial filling fraction. Heart rate was measured simultaneously. E/A ratios $<0.6$ and $>1.5$ were considered abnormal, representing the 5th and 95th percentiles of a reference range in 124 SHS participants (mean age, 58 years; 78 women) who had normal BP (mean, 113/69 mm Hg), normal body weight (body mass index [BMI] <25 kg/m$^2$), and no prevalent heart disease and were taking no cardiovascular medications. We have previously derived regression equations to predict the E/A at the leaflet tips by using measurements obtained from the annulus ($R=0.82$, $SEE=0.21$, $P<0.001$). Annu-

Calculation of Derived Variables

End-diastolic LV dimensions were used to calculate LV mass by a formula that yields values closely correlated with necropsy LV weight and that showed good reproducibility. LV mass was considered as an unadjusted variable and after adjusting for height to its allometric relation with LV mass (height$^{19}$) and for fat-free mass, LV mass/height$^{20}$ partition values of 49.2 g/m$^2$ (men) and 46.7 g/m$^2$ (women) were used to define LV hypertrophy. Relative wall thickness was calculated as posterior wall thickness/LV internal radius.

Clinical End Points

For survival analyses, observation began on the date of echocardiography, with verified data updated through December 1998. Deaths were identified from sources in each community and through annual follow-up of participants and verified through death certificates and review of medical records; only 7 participants (0.2%) were lost to follow-up. Deaths were classified as cardiac if caused by myocardial infarction and as sudden death from CHD or CHF, as previously described. by an independent review panel of physicians who were unaware of the echocardiographic findings.

Statistical Analyses

Data were analyzed using SPSS 9.0 (SPSS, Inc) software. Data are presented as mean$\pm$SD for continuous variables and proportions for categoric variables. The $\chi^2$ test was used to determine categoric variable differences, whereas the general linear model with Sidak’s post hoc test was used to determine continuous variable differences among groups. Cox proportional hazards analyses were used to determine relative risks of all-cause and cardiac death with E/A $<0.6$ or $>1.5$, after adjusting for age, sex, BMI, systolic BP, HDL and LDL cholesterol, hypertension, diabetes, current smoking, baseline CHD, LV hypertrophy and low EF ($<40$%). A 2-tailed $P<0.05$ indicated statistical significance.

Clinical Features

Of the 3008 SHS participants in the present analysis, most were women (64%), and the mean age was 60$\pm$8 years; 2429 (81%) participants had normal E/A, 490 (16%) had E/A $<0.6$, and 89 (3%) had E/A $>1.5$. The proportion of women was higher in low E/A than in normal or high E/A groups (Table 1). Participants with E/A $<0.6$ were on average older, whereas those with E/A $>1.5$ were younger than those with normal E/A. Those with E/A $<0.6$ or $>1.5$ had lower BMIs than did those with normal E/A ratio. Systolic BP was slightly higher among participants with low E/A than with normal or high E/A, whereas diastolic BP was slightly lower in those with high E/A than in the other groups; thus, pulse pressure was elevated in both groups with abnormal E/A. Heart rate was slightly higher in participants with low E/A than in those with normal or high E/A.

Patients with low E/A had higher prevalences of hypertension and diabetes than did participants with normal or high E/A, although the difference in prevalence of hypertension between the groups with low versus high E/A was not statistically significant. Baseline CHD was 2-fold higher and 4-fold higher among participants with E/A $<0.6$ or $>1.5$ than in those with normal E/A. CHF was twice as prevalent in participants with E/A $<0.6$ and $>8$-fold higher in those with E/A $>1.5$ than in those with normal E/A. The prevalence of mitral regurgitation was nearly 3-fold higher in participants with E/A $>1.5$ than in those with normal E/A, and was lowest in participants with E/A $<0.6$. In contrast, aortic regurgitation was nearly twice as prevalent in participants with E/A ratio E/A $<0.6$ or $>1.5$ than in those with normal E/A. Hypercholesterolemia status did not differ among groups. Prevalence of current smokers was lower in participants with E/A $<0.6$ than the other 2 groups.

LV Geometry and Function

Septal and posterior wall thicknesses were higher, whereas LV chamber size was smaller in participants with low E/A than in those with normal or high E/A (Table 2). Although there was no difference in septal or posterior wall thickness between groups with normal or high E/A, LV chamber size was largest in participants with E/A $>1.5$. Although absolute LV mass was statistically equivalent in the groups with low or normal E/A, LV mass/height$^{27}$ was higher with E/A $<0.6$. Absolute and indexed LV mass were higher in participants with E/A $>1.5$ than in those with E/A $<0.6$. Relative wall thickness was highest in participants with E/A $<0.6$ and
lowest in those with E/A > 1.5. As a result, the prevalences of concentric LV remodeling and concentric and eccentric LV hypertrophy were 6.7%, 7.4%, and 25.8%, respectively, among participants with E/A < 0.6, compared with 2.2%, 1.7%, and 21.2%, respectively, among those with normal E/A ratio and 1.1%, 0%, and 40.2%, respectively, among those with E/A > 1.5 (all P < 0.001).

Compared with participants with normal or low E/A, those with E/A > 1.5 had lower EF. As expected, participants with E/A < 0.6 had longer deceleration times and higher atrial filling fractions; those with E/A > 1.5 had shorter deceleration times and lower atrial filling fractions.

**All-Cause and Cardiac Mortality**

All-cause mortality was > 2-fold higher in both groups with abnormal E/A compared with those with normal E/A (Figure 1, left). A similar relation was observed between abnormal E/A and likelihood of cardiac death (Figure 1, right). Furthermore, among participants with no history of CHF at baseline, all-cause death rates were 2-fold higher with both E/A < 0.6 and E/A > 1.5 than with normal E/A (14.5 and 20.2 versus 7.8%; P < 0.001). Similarly, cardiac death rates were 2- and 4-fold higher among those with E/A < 0.6 and E/A > 1.5 than those with normal E/A (5.1% and 11.2% versus 2.1%; P < 0.001) in this group.

Because most previous data relating E/A ratio were obtained in individuals with reduced EF, mortality rates were analyzed separately among SHS participants with EF < 40% or ≥ 40%. Among participants with EF < 40%, both E/A < 0.6 and E/A > 1.5 groups had higher all-cause (37.5% and 52.9% versus 30.6%) and cardiac mortality rates (25.0% and 35.3% versus 10.2%; all P < 0.05). More significantly, among participants with EF ≥ 40%, both E/A < 0.6 and E/A > 1.5 were associated with 2- to 3-fold higher all-cause (14.0% and 12.5% versus 7.4%) and cardiac mortality rates (4.8% and 5.6% versus 1.9%; all P < 0.001).

After adjusting for age, sex, BMI, systolic BP, HDL and LDL cholesterol, the presence of hypertension, diabetes,

### TABLE 1. Baseline Clinical Characteristic of SHS Participants Grouped by E/A Ratio

<table>
<thead>
<tr>
<th>Variable</th>
<th>E/A &lt; 0.6 (n=400)</th>
<th>E/A 0.6–1.5 (n=2429)</th>
<th>E/A &gt; 1.5 (n=89)</th>
<th>P E/A &lt; 0.6 vs E/A &gt; 1.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, %</td>
<td>69</td>
<td>63</td>
<td>53</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Age, y</td>
<td>64±8</td>
<td>59±8</td>
<td>57±7</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30.5±5.8</td>
<td>31.3±6.1</td>
<td>28.6±5.4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>135±23</td>
<td>129±19</td>
<td>130±27</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>75±11</td>
<td>75±10</td>
<td>73±12</td>
<td>NS</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>60±18</td>
<td>54±17</td>
<td>57±21</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>72±10</td>
<td>67±9</td>
<td>66±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>60</td>
<td>43</td>
<td>49</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>69</td>
<td>52</td>
<td>48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>38</td>
<td>38</td>
<td>33</td>
<td>NS</td>
</tr>
<tr>
<td>CHD, %</td>
<td>9</td>
<td>4</td>
<td>16</td>
<td>NS</td>
</tr>
<tr>
<td>CHF, %</td>
<td>4</td>
<td>2</td>
<td>16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mitral regurgitation, %</td>
<td>19</td>
<td>25</td>
<td>64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aortic regurgitation, %</td>
<td>16</td>
<td>9</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>23</td>
<td>32</td>
<td>32</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS indicates not significant.

### TABLE 2. Baseline Left Ventricular Geometry and Function in SHS Participants Grouped by E/A Ratio

<table>
<thead>
<tr>
<th>Variable</th>
<th>E/A &lt; 0.6</th>
<th>E/A 0.6–1.5</th>
<th>E/A &gt; 1.5</th>
<th>P E/A &lt; 0.6 vs E/A &gt; 1.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septal thickness, cm</td>
<td>0.97±0.15</td>
<td>0.92±0.11</td>
<td>0.94±0.16</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LV internal diameter, cm</td>
<td>4.85±0.52</td>
<td>4.97±0.48</td>
<td>5.35±0.59</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Posterior wall thickness, cm</td>
<td>0.89±0.11</td>
<td>0.86±0.09</td>
<td>0.88±0.10</td>
<td>NS</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>160±41</td>
<td>158±39</td>
<td>187±59</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LV mass/height², g/m²</td>
<td>44±11</td>
<td>41±10</td>
<td>48±15</td>
<td>NS</td>
</tr>
<tr>
<td>LV mass/fat-free mass, g/kg</td>
<td>3.26±0.73</td>
<td>3.04±0.74</td>
<td>3.50±1.20</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.37±0.06</td>
<td>0.35±0.04</td>
<td>0.32±0.04</td>
<td>NS</td>
</tr>
<tr>
<td>EF, %</td>
<td>63±9</td>
<td>63±8</td>
<td>54±15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deceleration time, ms</td>
<td>230±80</td>
<td>199±62</td>
<td>151±57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial filling fraction</td>
<td>0.49±0.08</td>
<td>0.39±0.08</td>
<td>0.24±0.07</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NS indicates not significant.
CHD, current smoking, LV hypertrophy, and low EF, the relative risk of all-cause death for SHS participants with E/A >1.5 was 2.8 (95% CI, 1.19 to 6.75; P<0.05) (Figure 2A). In this model, E/A ≤0.6 was not independently associated with increased all-cause death (RR = 1.23; 95% CI, 0.83 to 1.62; P=0.19). After adjustment for age, sex, BMI, systolic BP, HDL and LDL cholesterol, presence of hypertension, diabetes, CHD, LV hypertrophy, and low EF, the relative risk of cardiac death in participants with E/A >1.5 was 2.8 (95% CI, 1.19 to 6.75; P<0.05) (Figure 2B), with no independent association with E/A ≤0.6 (RR = 1.18; 95% CI, 0.7 to 2.1; P=0.31). Reanalysis with the use of the derived E/A at the leaflet tips did not alter the results (data not shown).

Discussion

The present study is the first to examine the prognostic impact of the mitral E/A ratio in a population-based sample of middle-aged and elderly adults, while accounting for a wide range of potential confounding factors, including traditional risk factors and echocardiographic LV hypertrophy and low EF. Our study indicates that the E/A ratio, a simple method of assessing LV diastolic filling, is associated with cardiac mortality, independent of its clinical and echocardiographic correlates. Of perhaps greater significance, individuals with no history of CHF were as predisposed to increased cardiac mortality with E/A >1.5 as were those with CHF.

Clinical Correlates of Abnormal E/A Ratio

The association between age and impaired early diastolic relaxation is well described.1,2 In our study, those with E/A ≤0.6 were older, whereas those with E/A >1.5 were, on average, 10 years younger than those with normal E/A. It is possible that some participants with E/A >1.5 had truly normal diastolic filling. However, only 4% of participants with E/A >1.5 were normotensive, nonobese, nondiabetic, and free of clinical heart disease or LV hypertrophy. This suggests that most of the subjects in the high E/A group had a pseudonormal mitral filling pattern induced by elevated filling pressures. Although it has been reported that abnormal diastolic filling occurs in obese individuals,22 the present study of a population-based sample indicates that E/A ≤0.6 is associated with lower BMI, a particularly notable finding in view of the high prevalences in SHS participants of hypertension and diabetes, conditions associated with obesity. Additionally, participants with E/A >1.5 have lower BMIs than those with normal E/A or E/A ≤0.6. Further studies are needed to determine the impact of body composition on LV diastolic filling.

Our study confirms and extends previous observations about the association of hypertension and abnormal diastolic filling.2 In the present study, systolic BP was highest among those with E/A ≤0.6, and pulse pressure was modestly increased in both groups with abnormal E/A. Diabetes was more prevalent in the group with E/A ≤0.6, in addition to the expected high prevalence of hypertension.2 Similar to the Cardiovascular Health Study,2 we found associations between prevalent CHD or CHF and abnormal diastolic filling.

Prognosis of Abnormal E/A Ratio

Our study shows that E/A >1.5 is independently associated with decreased survival in this population-based sample of middle-aged and elderly adults. These results extend previous reports of associations between restrictive LV filling and poor outcome in patients with dilated cardiomyopathy5 or acute myocardial infarction.6 Our results identify an ~2-fold in-
crease in all-cause mortality and 3-fold increase in cardiac mortality associated with E/A >1.5 at baseline Doppler echocardiography. More importantly, our study indicates that the association of E/A >1.5 with cardiac mortality was present in individuals with no history of CHF and in those with EF ≥40%, suggesting that elevated filling pressures predispose to worse outcome, even in the absence of symptoms or significant systolic dysfunction. These individuals may benefit from more frequent follow-up and more aggressive treatment of conditions associated with abnormal diastolic filling or elevated LV filling pressures. Moreover, we have shown, for the first time, that increased cardiac death rates associated with E/A >1.5 are independent of traditional cardiac risk factors, including older age, male sex, smoking, HDL and LDL cholesterol, prevalent hypertension, diabetes, LV hypertrophy, and low EF. This is especially noteworthy because of the relatively short follow-up (average, 3 years) of this population-based sample.

We have also shown, for the first time, that E/A <0.6 is associated with higher all-cause and cardiac mortality rates in a population-based sample of middle-aged and elderly adults, indicating that severe relaxation impairment predisposes to worse outcome in older adults. However, after adjusting for covariates that included age and LV hypertrophy, E/A <0.6 was not an independent predictor of all-cause or cardiac death. It has been shown that a progressive decline in E/A ratio is associated with further deterioration in other parameters of LV relaxation, including prolongation of the deceleration and isovolumic relaxation times, marked systolic dominance of pulmonary venous inflow, and higher atrial reversal velocity.23 Thus, an E/A <0.6 indicates severe relaxation impairment. Because severe relaxation abnormalities occur commonly in older individuals with abnormal LV mass and geometry23,24 and who may have other cardiovascular risk factors, it is not surprising that a less striking association with E/A <0.6 was seen after covariate adjustment. However, we have also shown that the associated increased mortality rate with E/A <0.6 was present among those with no history of CHF at time of echocardiography, suggesting that an E/A <0.6 in otherwise healthy older adults may require further screening and intervention.

Clinical Implications

Studies have shown that half of instances of CHF in middle-aged and elderly adults are associated with abnormalities in diastolic function rather than systolic dysfunction.25,26 The fact that the association between abnormal E/A and decreased survival was present even in those with no history of CHF suggests that Doppler echocardiography may help identify older adults predisposed to adverse outcomes. We have recently shown that control of hypertension and regression of cardiac hypertrophy improve LV diastolic filling,27 but the impact of these interventions on survival requires further study.

Study Limitations

The E/A ratio used to assess diastolic filling and predict prognosis in this study was not obtained at the leaflet tips, as recommended by consensus statements,4 and thus may reflect volume flow rather than transvalvular gradients that better approximate interactions between chambers during diastole. To avoid excessive burden to SHS participants, no attempt was made to measure isovolumic relaxation time or assess pulmonary venous profiles. Thus, some individuals with pseudonormal filling pattern may be included in the normal E/A group. Although color flow mitral propagation velocity and tissue Doppler imaging of mitral annulus motion would have been useful to complement our assessment of diastolic filling, these newer modalities were not available at the time of study. The partition values that we used represented the 5th and 95th percentiles of an apparently normal subset of the population with similar age range and thus might not be generalizable beyond American Indian SHS participants.

Conclusions

In a population-based sample of middle-aged and elderly adults, mitral E/A >1.5 at baseline Doppler echocardiography is associated with 2-fold increased all-cause and 3-fold increased cardiac mortality rate independent of covariates; mitral E/A <0.6 was also associated with 2-fold increased all-cause and cardiac mortality rates but not independent of covariates.

Acknowledgments

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References


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