Age- and Gender-Specific Changes in the Left Ventricular Relaxation

A Doppler Echocardiographic Study in Healthy Individuals

Hiroyuki Okura, MD; Yuko Takada; Azusa Yamabe; Tomoichiro Kubo, MD; Koichiro Asawa, MD; Takeshi Ozaki, MD; Hiroyuki Yamagishi, MD; Iku Toda, MD; Minoru Yoshiyama, MD; Junichi Yoshikawa, MD; Kiyoshi Yoshida, MD

Background—Although left ventricular diastolic function has been shown to deteriorate with advancing age, its gender-specific change is unknown. The aim of this study was to investigate age- and gender-specific changes in tissue Doppler–derived left ventricular diastolic index, E′.

Methods and Results—A total of 1333 healthy individual without known heart disease or hypertension (mean age, 55 years; range, 10 to 89) were enrolled and studied. Peak early mitral annular velocity (E′) and peak late mitral annular velocity (A′) were recorded and measured. As an index of the left ventricular relaxation, E′ was used. As an index of the left ventricular filling pressure, E/E′ was calculated. Although systolic indices poorly correlated with age, diastolic indices correlated well with age. Among those aged 30 to 39 and 40 to 49 years, E′ was significantly lower in males than in females. In subjects aged 50 to 59 and 60 to 69 years, E′ was similar in both genders. Among those aged 70 to 79 and 80 to 89 years, E′ was significantly lower in females than in males. Predictors of the lowest quartile of E′ among subjects aged >50 years were age (P<0.0001;χ²=66.11; odds ratio, 1.08; 95% CI, 1.058 to 1.097) and female gender (P=0.002; χ²=9.23; odds ratio, 1.68; 95% CI, 1.202 to 2.343).

Conclusion—Age-related changes in diastolic indices were gender specific. In the elderly population, diastolic function deteriorated more significantly in the male gender than in the female gender. These results may explain the relatively higher incidence in elderly females among patients with diastolic heart failure and higher cardiovascular mortality in the female gender. (Circ Cardiovasc Imaging. 2009;2:41-46.)

Key Words: aging ■ diastole ■ echocardiography ■ ultrasonics ■ women

Over the past 20 years, the number of cardiovascular deaths for women has exceeded those for men in the United States.1 Gender-specific differences in the cause or prognosis of heart failure may, in part, explain this excess mortality in women.2 Pathophysiological and clinical presentation of women with heart failure may be different from those of men.2–3 In women, heart failure tend to be associated with impaired diastolic function or diastolic heart failure rather than systolic heart failure, which is a predominant cause of heart failure in men.1–6

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Tissue Doppler imaging (TDI) technology has become one of the standard methods to assess left ventricular (LV) diastolic function and provide pathophysiological as well as prognostic insight into systolic and diastolic heart failure.7–11 Although age-related changes in LV diastolic indices have been reported,12 gender-specific differences in LV diastolic indices throughout the entire age groups are poorly understood.13

Accordingly, we hypothesized that gender-related differences in LV diastolic function may present and possibly explain the gender-specific cause and prognosis of heart failure. Therefore, we investigated age and gender differences in LV diastolic indices derived from TDI in apparently healthy subjects.

Methods

Two thousand fifteen apparently healthy subjects without history of hypertension or heart disease who were sent for screening echocardiographic examination were initially selected from 16 405 consecutive patients who were sent for various reasons between May 2002 and July 2007. Those with atrial fibrillation (n=57) and other arrhythmias (n=151) at the time of the echocardiographic examination were excluded. Also, those with myocardial infarction (n=19), cardiomyopathy (n=8), congenital heart disease (n=5), and significant (>moderate) valvular heart disease (n=442) diagnosed by the...
echocardiographic examination were excluded. Finally, a total of 1333 healthy individuals without heart disease or hypertension (mean age 55 years; range, 10 to 89) were enrolled and studied.

Echocardiographic Examination

Echocardiographic examination was performed with a commercially available machine (Vivid 7, GE Medical) using a broad band transducer (S3). Two experienced sonographers (Y.T. and A.Y.) performed echocardiographic examinations and data collection. They were unblinded to the clinical information but blinded to the present study protocol.

After conventional echocardiographic examination, TDI was performed from apical 4 chamber view. Pulsed wave Doppler method was applied to obtain mitral annular velocity of the septal side. Peak systolic mitral annular velocity ($E'$) during ejection was measured as an index of the LV systolic function. Peak early mitral annular velocity ($E'$) and peak late mitral annular velocity ($A'$) were recorded and measured. As an index of the LV relaxation, $E'$ was used. As an index of the LV filling pressure, $E'/E$ was calculated. Intraobserver and interobserver variability of the $E'$ measurement was evaluated in 50 patients. Intraobserver variability was 5.1\% 6.0\% and interobserver variability was 8.2\%-8.0\%, respectively. Intraclass correlation coefficient for intraobserver and interobserver agreement were 0.95 and 0.94, respectively.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Statistical Analysis

Study subjects were categorized into each decade. Continuous variables were expressed as mean±SD, and categorical variables were presented as frequencies. Continuous categorical measures compared with $t$ test ANOVA, or $\chi^2$ test, as appropriate. The association between echocardiographic indices and age was investigated with linear regression and linear least-squares regression. Study subjects were also grouped into quartiles according to the $E'$ value. Logistic regression analysis was performed to identify predictors of the lowest quartile of $E'$. A probability value of <0.05 was considered as significant.

Results

Overall Results

Echocardiographic indices among all age groups are shown in Table 1 (2 dimensional echocardiographic indices) and Table 2 (Doppler echocardiographic indices). There were weak or poor linear correlations between age and LV end-diastolic dimension ($r=0.30; P<0.0001$), LV end-systolic dimension ($r=0.31; P<0.0001$), left atrial dimension ($R=0.19; P<0.0001$), LV end-diastolic volume ($R=0.47; P<0.0001$), LV end-systolic volume ($r=0.43; P<0.0001$), and ejection fraction ($r=0.08; P<0.0001$). There was no significant correlation between age and LV mass ($r=0.01; P=0.70$). Figure 1 demonstrates relationship between LV systolic indices (ejection factor and $S'$) and age. Both ejection factor ($r=0.08; P=0.04$) and $S'$ ($r=0.20; P<0.0001$) poorly correlated with age. Overall, relationship between age and LV diastolic indices are shown in Figures 2 and 3. Figure 2 shows the relationship between conventional Doppler derived LV diastolic indices and age. $E'(r=0.47; P<0.0001)$ and $E'/A'(r=0.75; P<0.0001)$ correlated negatively and significantly with age. On the other hand, $A'(r=0.66; P<0.0001)$ and deceleration time of $E'(r=0.34; P<0.0001)$ correlated positively and significantly with age. Figure 3 shows relationship between tissue Doppler–derived diastolic indices and age. $E'$ correlated negatively and significantly with age ($r=0.75; P<0.0001$). On

![Table 1. Two-Dimensional Echocardiographic Results From 1333 Healthy Subjects](http://circimaging.ahajournals.org/)

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>M/F</td>
<td>29/18</td>
<td>38/40</td>
<td>84/83</td>
<td>103/69</td>
<td>111/164</td>
<td>146/177</td>
<td>96/98</td>
<td>23/54</td>
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<tr>
<td>LVd, mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>M</td>
<td>47.3±3.1</td>
<td>46.1±11.2</td>
<td>47.7±3.5</td>
<td>46.2±7.2</td>
<td>44.5±6.7</td>
<td>45.2±5.1</td>
<td>43.6±4.7</td>
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<td>F</td>
<td>44.6±2.5</td>
<td>43.9±4.0</td>
<td>43.0±3.9</td>
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<td>42.3±5.5</td>
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<tr>
<td>LVd, mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>M</td>
<td>28.0±2.9</td>
<td>29.1±2.9</td>
<td>29.1±2.9</td>
<td>27.0±4.9</td>
<td>26.6±3.5</td>
<td>26.1±6.1</td>
<td>25.4±3.9</td>
<td>25.3±3.0</td>
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<tr>
<td>F</td>
<td>25.8±2.3</td>
<td>27.1±3.8</td>
<td>25.4±2.9</td>
<td>27.0±3.5</td>
<td>25.7±2.9</td>
<td>25.1±3.3</td>
<td>24.6±3.5</td>
<td>24.1±3.8</td>
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<tr>
<td>LAD, mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>M</td>
<td>31.1±4.1</td>
<td>31.0±3.3</td>
<td>33.7±3.2</td>
<td>34.2±3.6</td>
<td>33.5±5.7</td>
<td>33.9±3.7</td>
<td>33.7±3.8</td>
<td>30.1±8.4</td>
</tr>
<tr>
<td>F</td>
<td>29.8±2.7</td>
<td>29.2±3.3</td>
<td>30.6±4.1</td>
<td>32.3±3.6</td>
<td>33.1±3.8</td>
<td>33.5±4.8</td>
<td>32.9±4.4</td>
<td>32.6±4.7</td>
</tr>
<tr>
<td>LVEDV, mL</td>
<td>88.5±15.2</td>
<td>90.6±13.1</td>
<td>85.4±15.5</td>
<td>81.5±16.0</td>
<td>73.9±16.0</td>
<td>70.6±16.4</td>
<td>63.0±13.2</td>
<td>60.9±17.4</td>
</tr>
<tr>
<td>LVESV, mL</td>
<td>83.8±19.7</td>
<td>69.9±15.9</td>
<td>66.4±14.1</td>
<td>67.7±12.6</td>
<td>64.2±14.2</td>
<td>56.6±12.9</td>
<td>53.9±15.3</td>
<td>48.3±12.6</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>120.3±28.0</td>
<td>131.0±40.9</td>
<td>138.9±25.9</td>
<td>136.9±36.2</td>
<td>129.5±40.7</td>
<td>135.8±33.0</td>
<td>131.3±34.9</td>
<td>131.9±39.1</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. M indicates male; F, female; LVD, left ventricular dysfunction; LAD, left anterior descending; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; EF, ejection fraction.
Among those aged between 10 to 19 and the other hand, A \( r = 0.36; P < 0.0001 \) and E/E \( r = 0.48; P < 0.0001 \) correlated positively and significantly with age.

**Gender-Specific Changes in Diastolic Indices**

Comparison between men and women in each age group are shown in Figure 4. Among those aged between 10 to 19 and 20 to 29 years, E' was similar between male and female. E' progressively decline with advancing age in both gender, but more so in male than in female until age 50. As a result, E' was significantly lower in male than in female among those aged between 30 to 39 and 40 to 49 years. In subjects with age 50 to 59 and 60 to 69 years, E' was similar in male and female. After 70 years, E' decline more so in female than in male. As a result, E' was significantly lower in female than in male between age 70 to 79 and 80 to 89 years, suggesting that LV relaxation was more significantly impaired in women.
than in men among elderly subjects. E′ correlated negatively and significantly with age in both male (r=0.70; P<0.0001) and female gender (r=0.78; P<0.0001).

Predictors of the Impaired LV Relaxation
Study population was further divided into quartiles, according to the E′ value (Table 3). Overall (n=1333), predictors of the lowest quartile of E′ (E′<5.50 cm/s) were age (P<0.0001; χ²=207.98; odds ratio [OR], 1.10; 95% CI, 1.09 to 1.11) and female gender (P=0.01; χ²=6.30; OR, 1.45; 95% CI, 1.09 to 1.94). Among those <50 years (n=464), age (P<0.0001; χ²=60.24; OR, 1.15; 95% CI, 1.11 to 1.20) was a predictor of the lowest quartile of E′ (E′<8.09 cm/s), and male gender was a borderline predictor of the lowest quartile of E′ (P=0.06; χ²=3.64; OR, 1.59; 95% CI, 0.99 to 2.56). On the other hand, age (P<0.0001; χ²=66.11; OR, 1.08; 95% CI, 1.06 to 1.10) and female gender (P=0.002; χ²=9.23; OR, 1.68; 95% CI, 1.20 to 2.34) were predictors of the lowest quartile of E′ (E′<4.96 cm/s) among those ≥50 years (n=869).

Discussion
The principal finding of this study is that age-related changes in diastolic indices were gender specific. In the elderly population, diastolic function deteriorated more significantly in female gender than in male. These results may explain the relatively higher incidence in elderly female among patients with diastolic heart failure4–6,14 and higher cardiovascular mortality in female gender.1

Age-related decline in LV diastolic function has been widely reported using conventional Doppler method. Miyatake et al12 has shown that LV inflow derived E and E/A decreased with advancing age among normal subjects. Although prognostic impact of the diastolic indices in healthy subjects are unknown, diastolic indices are related to exercise capacity.15 More recently, similar age-related changes in LV diastolic indices derived from tissue Doppler imaging have been reported.16 Munagala et al16 demonstrated that E′ decreased with advancing age, reflecting impaired LV relaxation. Our present results not only confirmed their results with larger population but also addressed gender-specific differences in the age-related changes.

Gender-specific differences in LV diastolic function have not been well investigated and reported. Our present results may suggest that postmenopausal status may be related to impaired LV relaxation. In fact, natural menopause usually occurs some
time between the age of 45 and 55, which is exactly the same period as LV relaxation in female fall below male. Estrogen has been shown to have direct vasodilator effect on arterial system.\textsuperscript{17,18} In addition, estrogen promote nitric oxide excretion.\textsuperscript{19,20} Further, estrogen have inhibitory effects on smooth muscle cell proliferation.\textsuperscript{21} Lack of these favorable effects of the estrogen in the elderly female may be related to the impaired LV relaxation in postmenopausal elderly women. Another possible reason for the more decline in E‘ in elderly female is that they tend to live longer than male. However, it is unknown weather male gender with impaired LV relaxation passed away earlier than female gender.

Hormone replacement therapy may theoretically improve LV diastolic function and thereby improve outcome of the postmenopausal women with heart failure. In fact, results from clinical trials did support that estrogen replacement improve LV diastolic function and/or prognosis.\textsuperscript{22,23} On the other hand, possible harmful effects of the hormone replacement therapy (HRT) on atherosclerotic progression have been reported.\textsuperscript{24,25} Therefore, it is inconclusive whether routine use of HRT is recommended in postmenopausal women with impaired LV relaxation. None of our study population was on HRT at the time of the echocardiographic study.

Our present results may have implication on the increased incidence of diastolic heart failure among elderly women. Epidemiological and clinical studies have consistently demonstrated that elderly women were predominant population among patients with diastolic heart failure.\textsuperscript{14,26} Importantly, patients with diastolic heart failure have similar or marginally better prognosis than those with systolic heart failure.\textsuperscript{26} Further, despite the continuous improvement in prognosis among patients with systolic heart failure, prognosis of the patients with diastolic heart failure did not improve over the past decade or so.\textsuperscript{27} Similarly, a large population-based study showed improved survival in elderly (>65 years) men between 1970 to 1974 and 1990 to 1994, but no change in survival was observed for women.\textsuperscript{28} This may be related to the lack of our understanding of the baseline pathophysiologic background of the patients with diastolic heart failure. Our present results may further improve our understanding of this commonly observed but little understood disease entity.

### Table 3. Predictors of the Impaired LV Relaxation

<table>
<thead>
<tr>
<th>Predictors of the Lowest Quartile of E’</th>
<th>P Value</th>
<th>$\chi^2$</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n=1333) Age</td>
<td>&lt; 0.0001</td>
<td>207.98</td>
<td>1.10</td>
<td>1.09–1.11</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.01</td>
<td>6.30</td>
<td>1.45</td>
<td>1.09–1.94</td>
</tr>
<tr>
<td>Age &lt;50 years (n=464) Age</td>
<td>&lt; 0.0001</td>
<td>60.24</td>
<td>1.15</td>
<td>1.11–1.20</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.06</td>
<td>3.64</td>
<td>1.59</td>
<td>0.99–2.56</td>
</tr>
<tr>
<td>Age ≥50 years (n=869) Age</td>
<td>&lt; 0.0001</td>
<td>66.11</td>
<td>1.08</td>
<td>1.06–1.10</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.002</td>
<td>9.23</td>
<td>1.68</td>
<td>1.20–2.34</td>
</tr>
</tbody>
</table>

### Limitations

There are several limitations of this study. First, although we discussed possible relationship between estrogen and LV diastolic function, the exact menstrual status as well as estrogen concentration of our study population is unknown. Therefore, the relationship among menstruation status, estrogen, and the LV relaxation needs to be investigated. Second, impact of diastolic heart dysfunction on prognosis in apparently healthy study population is unknown and therefore needs to be investigated further. Third, because only septal mitral annular velocity has been routinely measured, our results may not be generalized to the Doppler value obtained from lateral mitral annulus. In general, E‘ obtained from lateral mitral annulus tend to be higher and E/E‘ tend to be lower than those from septal mitral annulus. Although lateral mitral annular velocity and thus average mitral annular velocity were available in only a subset of the study population, similar gender specific age-related changes were observed (data not shown). Fourth, because multiple comparisons of age groups were conducted without adjustment for multiplicity, possibility of the type 1 error could not be eliminated. Finally, although known history of heart disease, hypertension were excluded from our healthy subjects, subclinical condition that may affect LV diastolic function could not be completely excluded. For example, impaired glucose tolerance may be related to early deterioration of the LV relaxation in middle-aged subjects.\textsuperscript{29}

### Conclusions

Age-related deterioration in the LV diastolic indices is gender specific. Worse LV diastolic indices observed in elderly women may explain gender-specific difference in the cause of heart failure.

### Disclosures

None.

### References


CLINICAL PERSPECTIVE

This study investigated age- and gender-specific changes in tissue Doppler-derived index of the left ventricular relaxation, **E’**, in 1330 apparently healthy individuals (ages, 10 to 89 years). Although left ventricular systolic indices correlated poorly with age, left ventricular diastolic indices, including **E’**, correlated well with age, as reported previously. Interestingly, **E’** was significantly lower in males than in females among those aged 30 to 39 and 40 to 49 years and significantly higher in males than in females among those aged 70 to 79 and 80 to 89 years. Otherwise, **E’** was similar between male and female genders. Female gender and age were independent predictors of impaired left ventricular relaxation among subjects aged >50 years. These gender-specific, age-related changes in diastolic indices may explain the relatively higher incidence in elderly females among patients with diastolic heart failure and higher cardiovascular mortality in the female gender. Thus, the results of this study will help us understand gender difference in the cause of heart failure. Further study to identify gender-specific determinants of the impaired left ventricular relaxation should be investigated in healthy subjects as well as in patients with cardiac diseases.
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