Factors of importance to Doppler indices of left ventricular filling in 50-year-old healthy subjects

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Age is an important determinant of Doppler indices of left ventricular diastolic filling in normal subjects. To define reference values and factors of importance to Doppler indices of left ventricular filling in subjects of similar age, 58 men and 76 women aged 50 years underwent Doppler echocardiography. All those taking part in the study were healthy. When gender was analysed in a multivariate model it showed a significant independent correlation with the peak velocity of early diastolic filling (E wave) (P<0.001) and the early to atrial peak velocity (E/A) ratio (P<0.01). The peak E wave velocity was 0.75 ± 0.11 m.s⁻¹ vs 0.66 ± 0.10 m.s⁻¹ (P<0.001) and the E/A ratio was 1.24 ± 0.25 vs 1.14 ± 0.20 (P<0.05) in women and men, respectively. In multivariate analyses, heart rate, diastolic blood pressure and body mass index correlated independently with the E/A ratio in women (P<0.001 for all), whereas in men, heart rate, diastolic blood pressure, body mass index and left ventricular diameter correlated independently with the E/A ratio (P<0.001 for all). Doppler measurements of left ventricular filling in 50-year-old healthy subjects showed a wide variation and were significantly associated with heart rate, diastolic blood pressure, body mass index and gender.

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Key Words: Diastolic Doppler indices, healthy subjects, similar age.

Introduction

Diastolic filling abnormalities are seen in many patients with various cardiac diseases. Diastolic left ventricular function is routinely assessed by Doppler echocardiography. Left ventricular stiffness and relaxation are important primary determinants of left ventricular filling, and hypertension, loading conditions and valvular heart disease also influence Doppler left ventricular filling indices.

Age is an important determinant of Doppler indices of left ventricular filling in healthy subjects. To distinguish properly between diastolic dysfunction and normal physiological variations in left ventricular filling indices in different age groups, it is important to define reference values of Doppler left ventricular filling indices, based on large samples of similarly aged healthy subjects. In prior studies of Doppler measurements of left ventricular filling in healthy subjects, there was a considerable variation in age among the investigated subjects. No study has, to our knowledge, reported normal values and important determinants of Doppler indices of left ventricular filling in a group of similarly aged subjects. The purpose of this study was to describe reference values for Doppler diastolic indices and to analyze the influence of factors other than age on Doppler indices of left ventricular filling, in a group of 50-year-old healthy subjects.

Methods

Study population

From 1990 to 1992 in the county of Västmanland, Sweden, a study was performed of the prevalence of effort-induced chest pain in subjects aged 50 years. The Rose-Blackburn questionnaire was used for assessment of chest pain. An age-matched control group of women and men without chest pain was selected. From this group of 250 subjects, 134 (76 women and 58 men) underwent Doppler echocardiography. All were healthy and used no regular medication.

Exclusion criteria were: angina pectoris, myocardial infarction, valvular heart disease, atrial fibrillation, left bundle branch block, hypertension, diabetes mellitus, hypertrophic cardiomyopathy, dilated cardiomyopathy, other chronic cardiac or non-cardiac disease. In addition, subjects with the following echocardiographic findings were excluded: valvular abnormalities, left ventricular abnormalities (dilation, wall motion...
abnormalities) or technically inadequate echocardiograms. Mild isolated left ventricular hypertrophy was not an exclusion criteria, but none of the subjects had a left ventricular wall thickness >13 mm. The study protocol was approved by the ethics committee and each subject in the study gave verbal informed consent.

Subject characteristics
All subjects were 50 years of age. They were interviewed about their physical activity and smoking habits. Systolic and diastolic blood pressures (mmHg) were measured after 10 min rest in the supine position. Heart rate was measured from Doppler recordings. Body mass index (weight in kg . height \(^{-1}\) in m\(^2\)) was used as a measure of obesity.

Echocardiography and Doppler studies
The subjects were examined with an Apogee CX 100, Interspec ultrasound machine. The transducer frequency was 2.75 MHz for two-dimensional imaging and 2.0 MHz for Doppler. M-mode, two-dimensional, continuous-wave Doppler, pulsed-wave Doppler and colour Doppler echocardiography were performed. An electrocardiogram was recorded simultaneously with the M-mode and Doppler tracings. All examinations were made by one physician.

The M-mode measurements were obtained according to the American Society of Echocardiography guidelines, using a leading-edge-to-leading-edge method\(^{18}\). If the M-mode was technically inadequate, two-dimensional measurements from the same view were used. Interventricular septal (IVS) thickness, left ventricular posterior wall (LVPW) thickness, left ventricular internal dimension at end-diastole (LVIDed) and left ventricular internal dimension at end-systole (LVIDes) were measured. Left ventricular fractional shortening was calculated as \((\text{LVIDes} - \text{LVIDed})/\text{LVIDed}\)^{\text{19}}, Left ventricular mass was calculated from the modified cubed formula: LV mass (g) = \(1.04((\text{LVIDed} + \text{IVS} + \text{LVPW})^3 - (\text{LVIDed})^3 - 13.67)\).

The Doppler examination of left ventricular inflow was performed during quiet respiration with the subjects in a left lateral recumbent position, using the apical four-chamber view with the sample volume between the mitral leaflet tips\(^{21}\). The cursor was lined up parallel to the left ventricular inflow to minimize the angle. The Doppler was recorded at a sweep speed of 100 mm . s\(^{-1}\) and consisted of five cardiac cycles. The following Doppler indices were measured directly on-line during the examination: peak early diastolic velocity (E-wave), peak atrial diastolic velocity (A-wave) and deceleration time of early velocity. The deceleration time was measured as the time from peak E velocity to the extrapolation of the decline of the velocity to the baseline value. The early to atrial peak velocity ratio (E/A ratio) was calculated. Three cycles were analysed and average values were calculated.

Table 1 Subject characteristics of the study group

<table>
<thead>
<tr>
<th></th>
<th>Men (n=58)</th>
<th>Women (n=76)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>67.4 ± 10.0</td>
<td>70.2 ± 10.3</td>
<td>0.06</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>134.0 ± 14.0</td>
<td>131.0 ± 17.0</td>
<td>0.14</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>85.2 ± 8.6</td>
<td>85.0 ± 9.0</td>
<td>0.45</td>
</tr>
<tr>
<td>Body mass index (kg . m(^{-2}))</td>
<td>25.4 ± 2.4</td>
<td>24.1 ± 3.0</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

The values are mean ± standard deviation.

Reproducibility was studied by examining 10 subjects twice at an interval of 4 to 6 months. The correlation coefficient of measuring the E/A ratio was 0.95 and the coefficient of variation was 5.8%.

Statistical analyses
Univariate associations were studied using Pearson's correlation coefficients. Group differences were studied with Student's t-test. Analysis of variance was used to evaluate differences in Doppler indices between women and men with correction for other factors that could be explained by differences in gender. Clinical and echocardiographic variables that could influence Doppler indices were entered in multivariate regression analyses, with Doppler indices considered as a dependent variable. Stepwise regression analyses with backwards elimination (P<0.10) were used. The square of the multiple correlation coefficient (R\(^2\)) was calculated for the total equation and the R\(^2\) change separately for each factor accepted into the model. These figures indicate how much of the variation in any Doppler index was explained by the total equation and each individual factor. Numerical data are presented as mean ± standard deviation.

Results

Subject characteristics (Table 1)
There were no significant differences between women and men with regard to heart rate, systolic or diastolic blood pressure, smoking habits or physical activity. The women had a slightly, but significantly, lower body mass index than the men.

M-mode echocardiography (Table 2)
Left ventricular dimension was significantly smaller in women than men. There was also a significant difference in wall thickness and left ventricular mass between women and men with correction for other factors that could be explained by differences in gender.
Table 2  M-mode echocardiographic measurements of the study group

<table>
<thead>
<tr>
<th></th>
<th>Men (n=58)</th>
<th>Women (n=76)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular diastolic diameter (mm)</td>
<td>49±4.1</td>
<td>46±3.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Interventricular septal thickness (mm)</td>
<td>10±1.1</td>
<td>9.3±1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Posterior wall thickness (mm)</td>
<td>10±1.1</td>
<td>9.2±1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular mass (g)</td>
<td>212±41.5</td>
<td>169±31.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fractional shortening</td>
<td>0.37±0.06</td>
<td>0.39±0.06</td>
<td>0.07</td>
</tr>
</tbody>
</table>

The values are mean ± standard deviation.

Figure 1  E/A ratio in women (upper panel) and men (lower panel). Note the variation of E/A ratio and the difference between women and men, with higher values in women. E/A ratio = early to atrial peak velocity ratio.

women and men, but not in left ventricular fractional shortening.

**Doppler indices of left ventricular filling (Table 3)**

The left ventricular inflow Doppler velocities and E/A ratio differed significantly between women and men. The peak early velocity E-wave was 0.75±0.11 m·s⁻¹ vs 0.66±0.10 m·s⁻¹ (P<0.001), the peak atrial velocity A-wave 0.63±0.13 vs 0.58±0.09 (P<0.05) and the peak velocity ratio E/A 1.24±0.25 vs 1.14±0.20 (P<0.05) in women and men, respectively. There was no significant difference in deceleration time of the E-wave. Total range for the E/A ratio was 0.78–2.18 in women vs 0.80–1.61 in men (Fig. 1).

**Determinants of Doppler indices of left ventricular filling (Tables 4 and 5)**

Univariate associations between Doppler indices of left ventricular filling and background factors are shown in Table 4 for women and men separately. There were no significant univariate associations between subject and M-mode echocardiographic characteristics and the deceleration time of early velocity.

Multivariate analyses revealed that gender was significantly associated with the peak early velocity E and E/A ratio. However, the partial R² value revealed that the variation in E/A ratio attributable to gender was only 3%.

In all the 134 subjects the multivariate model showed that gender, heart rate, body mass index, diastolic blood pressure and LV internal dimension were
Table 3 Doppler indices of left ventricular filling in men and women

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 58)</th>
<th>Women (n = 76)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak early diastolic velocity E (m.s⁻¹)</td>
<td>0.66 ± 0.10</td>
<td>0.75 ± 0.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak atrial velocity A (m.s⁻¹)</td>
<td>0.58 ± 0.09</td>
<td>0.63 ± 0.13</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Early to atrial peak velocity ratio (E/A)</td>
<td>1.14 ± 0.20</td>
<td>1.24 ± 0.25</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Deceleration time of E wave (ms)</td>
<td>195 ± 32</td>
<td>189 ± 29</td>
<td>0.14</td>
</tr>
</tbody>
</table>

The values are mean ± standard deviation.

Table 4 Determinants of Doppler indices of left ventricular filling in men and women. Univariate correlation coefficients

<table>
<thead>
<tr>
<th></th>
<th>E-wave</th>
<th>A-wave</th>
<th>E/A ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (n = 58)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>-0.14</td>
<td>0.12</td>
<td>-0.27**</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>-0.31**</td>
<td>0.31**</td>
<td>-0.57***</td>
</tr>
<tr>
<td>Heart rate</td>
<td>-0.10</td>
<td>0.53***</td>
<td>-0.54***</td>
</tr>
<tr>
<td>Body mass index</td>
<td>-0.08</td>
<td>0.40**</td>
<td>-0.42**</td>
</tr>
<tr>
<td>Left ventricular dimension</td>
<td>0.25*</td>
<td>-0.22*</td>
<td>0.41**</td>
</tr>
<tr>
<td>Left ventricular mass</td>
<td>0.14</td>
<td>-0.13</td>
<td>0.23*</td>
</tr>
</tbody>
</table>

|                      |        |        |           |
| Women (n = 76)       |        |        |           |
| Systolic blood pressure | -0.18 | 0.09  | -0.24*    |
| Diastolic blood pressure | -0.28**| 0.14  | -0.37**   |
| Heart rate           | -0.14 | 0.39***| -0.47***  |
| Body mass index      | -0.15 | 0.39***| -0.43***  |
| Left ventricular dimension | -0.05 | -0.14 | 0.11      |
| Left ventricular mass | -0.33**| -0.09 | -0.16     |

E-wave = peak early velocity (m.s⁻¹); A-wave = peak atrial velocity (m.s⁻¹); E/A ratio = early to atrial peak velocity ratio. *P<0.05, **P<0.01, ***P<0.001.

Discussion

We studied a healthy sample of 50-year-old women and men to describe reference values and factors influencing Doppler indices of left ventricular filling. Prior studies have reported that age is the most important determinant of Doppler diastolic filling measurements in healthy subjects[12-15], but as we studied subjects of similar age, we focused our interest on other factors of importance to Doppler indices of left ventricular filling.

Reference values

We found a wide variation in peak velocity E, peak velocity A, the E/A ratio and deceleration time of early velocity both in women and men. Prior investigators have described Doppler indices in subjects of different ages and the sample sizes of the subgroups born in the same decade were smaller[12-15].

Determinants of Doppler left ventricular filling indices

Previous studies have shown conflicting results concerning the association between gender and Doppler left ventricular inflow[12-14,22]. Benjamin et al.[12] found that the peak velocity E and the E/A ratio were greater in women than men. Voutilainen et al.[13] noted that the E/A ratio was smaller in women compared to men in a small group of middle-aged subjects. Other studies have not noted sex differences in Doppler indices of left ventricular filling[14,22]. The present investigation supports the findings of Benjamin et al.[21] that gender is a determinant of left ventricular filling in healthy subjects, with a greater E/A ratio in women.

Heart rate was positively and significantly associated with peak velocity A and inversely with the E/A ratio both in women and men. These findings agree with prior studies showing that heart rate is an important determinant of left ventricular diastolic inflow[12,13,23,24].

Some investigators have reported a weak association between systolic blood pressure and Doppler left ventricular filling[12,14], but we found no such independent association. Diastolic blood pressure was significant independent determinants of the peak velocity E/A ratio, with an inverse association between heart rate, body mass index, diastolic blood pressure and E/A ratio. The R² value revealed that these factors explained 43% of the variation in the E/A ratio (Table 5).

When women were analysed separately in a multivariate model the heart rate, body mass index and diastolic blood pressure were independent determinants of the E/A ratio and the R² value showed that these factors explained 34% of the variation in the E/A ratio (Table 5).

The independent determinants of the E/A ratio in men were diastolic blood pressure, heart rate, body mass index and left ventricular internal dimension. Left ventricular internal dimension was the only factor that was positively correlated with the E/A ratio. The R² value revealed that 53% of the variation in the E/A ratio was explained by these factors (Table 5).

The multivariate model showed no independent significant correlation between smoking habits or physical activity and Doppler indices of left ventricular filling.
significantly associated with Doppler indices of left ventricular filling in our study, with an inverse association between diastolic blood pressure and the E/A ratio in both women and men. The association was particularly strong in men. Previous studies have shown various results regarding the association between diastolic blood pressure and Doppler left ventricular filling indices. No significant correlation between diastolic blood pressure and Doppler transmural flow was seen in a group of healthy subjects of various ages from the Framingham study, and Gardin et al. also demonstrated an absence of this association. In another study, diastolic blood pressure was associated with Doppler left ventricular inflow, with a higher pressure correlating with a shift of filling to late diastole, which is confirmed by our study. The strong independent association in our study between diastolic blood pressure and the E/A ratio in healthy subjects could be explained by the fact that we studied a larger sample of similarly aged subjects. Altered Doppler indices of left ventricular filling have been reported in subjects with hypertension. Such subjects were thus excluded from our study.

Body mass index was significantly associated with peak velocity A and the E/A ratio in women and men. Peak velocity A increased and the E/A ratio decreased with increasing body mass index. A study by Zarich et al. reported altered Doppler indices of left ventricular filling in morbidly obese patients, with a reduction in the ratio between early and late peak velocities. Conflicting results have been reported in healthy subjects. Some investigators found no significant association between body mass index and left ventricular filling, while others reported that increased body mass index may impair left ventricular diastolic properties.

This study demonstrates that body mass index is an important determinant of left ventricular filling even in healthy subjects. The absence of this association reported by other investigators could be due to the variation in the age of the subjects studied, which could have concealed the association between body mass index and Doppler left ventricular filling indices.

The left ventricular internal dimension was positively and significantly correlated with the E/A ratio in men, but not in women. Prior studies have not noted this association separately in women or men. Previous investigators have not reported a significant effect of left ventricular mass on Doppler left ventricular filling in healthy individuals. However, the present study shows that the filling properties of the left ventricle seem, even in healthy subjects, to be dependent to some degree on the wall thickness and the dimension of the left ventricle. Some investigators found a weak association between left ventricular fractional shortening and Doppler diastolic filling. In our study, fractional shortening had no such association.

Deceleration time of early velocity was not significantly associated with the clinical variables and M-mode echocardiographic characteristics that we investigated. Several heart diseases influence the deceleration time of early mitral velocity, indicating deceleration time is influenced by cardiac disease and impaired diastolic function, but not by physiological factors in healthy subjects.

**The findings related to the physiology of diastole**

Thomas et al., using a mathematic model of left ventricular filling, showed that prolonged left ventricular relaxation time reduced peak early mitral velocity, and increased ventricular compliance caused higher peak
early velocity. A study by Appleton et al.\textsuperscript{[21]} correlated mitral flow velocity patterns with haemodynamic findings. In patients with normal left atrial pressure, it appeared that a reduced rate of left ventricular relaxation was the predominant factor, resulting in a mitral flow velocity pattern with a reduced early to atrial peak velocity ratio\textsuperscript{[21]}.

The findings in our study suggest that there is a physiological relationship between extra cardiac factors and the primary cardiac determinants of left ventricular diastolic function. Body mass index and diastolic blood pressure were inversely associated with the E/A ratio in the healthy subjects we studied, and men had a reduced E/A ratio compared with women. The reduction in the E/A ratio associated with body mass index, diastolic blood pressure and gender, may be attributed to the influence of these factors on the rate of left ventricular relaxation.

Increased heart rate resulted in higher atrial filling velocities and a reduced E/A ratio. Previous investigators have suggested several possible explanations for the interaction between heart rate and Doppler indices of left ventricular filling\textsuperscript{[24]}. An increase in heart rate might lead to reduced left ventricular relaxation, the loss of diastolic filling time may result in incomplete left atrial emptying before the onset of the atrial contraction and the left ventricle may be at a low point on its diastolic pressure–volume curve at the time of atrial contraction\textsuperscript{[26]}

In our study, left ventricular internal dimension was positively correlated with peak early velocity and E/A ratio in men, indicating a possible association between shortened left ventricular relaxation time or increased left ventricular compliance and left ventricular diastolic diameter.

### Study limitations

Increased left atrial and left ventricular filling pressure significantly influence Doppler left ventricular filling indices\textsuperscript{[21,29]}. Invasive measurements were not included in our study as we studied healthy subjects free of heart disease but it seems reasonable that left atrial pressure and left ventricular filling pressure were within normal limits.

In our study the subject's health was based on clinical data. Some of the subjects could have had occult coronary disease, although the risk in an asymptomatic group at this age, with normal systolic left ventricular function on echocardiography, was probably small\textsuperscript{[30]}

### Study advantages

All subjects in our study were 50 years of age. Age is the most important determinant of Doppler indices of left ventricular filling in healthy subjects\textsuperscript{[12-14,22]}. When subjects of different age are included in studies of Doppler diastolic filling, it is difficult to assess the importance of other factors, because age has such a dominant effect on Doppler diastolic values. Conflicting results of the importance of some possible determinants of Doppler diastolic filling indices have been reported\textsuperscript{[12-14,22]}, possibly caused by the variation in age in the study groups and the relatively small sample sizes of subjects of similar age. A group of subjects of uniform age should preferably be chosen, if determinants of diastolic Doppler velocities are to be studied. All examinations were made by one physician, giving a high reproducibility of the Doppler indices. The small variation that occurred might partially be explained by the difference in heart rate and the natural physiological variation caused by the period of time between the examinations.

### Conclusion

The availability of additional reference values in middle-aged subjects may be useful for proper identification of left ventricular diastolic dysfunction. When Doppler indices of left ventricular filling are interpreted, the wide physiological variation should be taken into consideration.

Gender, heart rate, body mass index, diastolic blood pressure and left ventricular internal dimension explained 43% of the variation in the E/A ratio in the whole study group of healthy subjects aged 50 years. In the women 34% and in the men 53% of the variation in the E/A ratio could be explained. The importance of these findings lie in uncovering the relationship between extra cardiac factors and the primary cardiac determinants of left ventricular filling. This suggests that there are other physiological relationships to be explored.

Further studies are needed to investigate the extent to which the factors described in our study influence Doppler diastolic left ventricular filling in patients with various heart diseases.

We thank Stefan Sörensen and Urban Niklasson for statistical advice, and Helena Elwin and Marie Louise Engström Walker for coordination of the study.

### References

[5] Spirito P, Maron BJ. Relation between extent of left ventricular hypertrophy and diastolic filling abnormalities in