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Decreased Aorto-septal Angle Contributes to Left Ventricular Diastolic Dysfunction in Healthy Subjects

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Running title: Aorto-septal angle and LV diastolic function

Conflict of interest: None to declare
ABSTRACT

Background: Left ventricular (LV) diastolic dysfunction is often observed in healthy older subjects without structural heart diseases. However, the exact mechanisms have not been established. A decrease in the aorto-septal angle (ASA), which represents an LV deformation due to aortic elongation, is also frequently seen in elderly subjects. The objective of this study was to evaluate whether a decrease in the ASA can contribute to LV diastolic dysfunction in healthy subjects.

Method: Echocardiography was performed in 77 healthy subjects (42 males, mean age 43.2 ± 13.8 years) to measure the ASA and the LV mass index (LVMI). The LV peak early diastolic longitudinal strain rate (GSR_E) was measured using a two-dimensional speckle tracking imaging technique.

Result: Age, body mass index (BMI), ASA, and LVMI were significantly correlated with the GSR_E, and the best correlation was observed between the ASA and the GSR_E (r = 0.63, p < 0.001). A stepwise multivariate analysis revealed that ASA and BMI were independent predictors of GSR_E, whereas age and LVMI were not.

Conclusion: LV deformation associated with a reduced ASA is one of the significant causes of LV diastolic dysfunction independently of age in otherwise healthy subjects.

Keywords: Aging, Aorto-septal angle, Left ventricular diastolic function, Left ventricular myocardial relaxation, Sigmoid septum
INTRODUCTION

Left ventricular (LV) diastolic dysfunction is often observed in healthy older subjects.\textsuperscript{1-6} Recent large-scale, community-based studies have shown that the presence and the degree of LV diastolic dysfunction is closely related to the incidence of heart failure and increased mortality in community population without any history of heart disease.\textsuperscript{7-9} Therefore, in order to stratify the risk of heart failure, it is important to understand the mechanisms of LV diastolic dysfunction in subjects without any structural heart diseases.

LV diastolic dysfunction in the elderly is due to abnormal myocardial cellular Ca\textsuperscript{2+}-handling, myocardial fibrosis, and increased arterial stiffness.\textsuperscript{10-15} However, these mechanisms were not concretely proved in human subjects, and the exact mechanisms of senile LV diastolic dysfunction have not yet been established. LV deformation, represented by a decrease in the aorto-septal angle (ASA), is also frequently observed in healthy older subjects, usually recognized as a minor innocent finding.\textsuperscript{16-20} Moreover, the pathophysiological role of such an LV deformation in the development of diastolic dysfunction has not been studied. The objective of the present study was to evaluate whether a decrease in the ASA can contribute to LV diastolic dysfunction in otherwise healthy subjects.

SUBJECTS AND METHODS

Study Subjects
The present study examined 77 healthy subjects (42 men and 35 women, age 43.2 ± 13.8 years) for whom good-quality echocardiographic images could be obtained. They consisted of 59 patients who underwent an echocardiographic examination in our laboratory and did not have any echocardiographic abnormalities or any history of cardiac or systemic diseases such as hypertension, diabetes mellitus or dyslipidemia, and 18 normal volunteers who agreed to participate in this study with written informed consent. This study was approved by both the Research Ethics Committee of Hokkaido University Hospital and the Ethics Committee of the Faculty of Health Sciences in Hokkaido University.

**Basic Echocardiographic Measurements**

Echocardiography was performed using a Vivid 7 or Vivid q echocardiographic machine (GE Healthcare UK, Buckinghamshire, England) equipped with an M4S transducer. The angle between the LV septal surface and the aorta (aorto-septal angle; ASA) was measured in the end-diastolic parasternal long-axis B-mode image (Fig. 1).\(^{17}\) The LV end-diastolic dimension (LVDd), the LV end-systolic dimension, and the left atrial end-systolic dimension were measured in the parasternal long-axis images. The thicknesses of the interventricular septum (IVST) and the LV posterior wall (PWT) were measured in the end-diastole parasternal short-axis images at the level of the chordae tendineae. The LV ejection fraction (LVEF) was calculated from the apical two-chamber and four-chamber images using the biplane disk-summation method along with the guidelines of the American Society of Echocardiography.\(^{21}\) LV mass was calculated using the following equation: 0.8 × \{1.04 [(IVST + LVDd + PWT)\(^3\) − (LVDd)\(^3\)]\} + 0.6.\(^{22}\) LV mass was indexed for each subject's body surface area (LVMI).
Pulsed-Doppler echocardiography was performed to measure peak early- and late-diastolic transmitral flow velocities (E and A, respectively, m/s) and the early-diastolic wave deceleration time (DT, msec) of the transmitral flow, and to calculate the ratio of the early to late transmitral flow velocities (E/A). The LV isovolumic relaxation time (IRT, msec) was measured from an apical continuous-wave Doppler recording which depicted both LV inflow and outflow. Tissue Doppler imaging of the mitral annulus was performed in the apical four-chamber view, and the peak early-diastolic annular velocity (e’) was measured at the interventricular septal annulus.

Two-dimensional Speckle Tracking Imaging Analysis

Digital cine loops of apical long-axis images were obtained under a breath-hold in shallow expiration and stored on the hard disk of the echocardiographic machine. They were transferred to a workstation (EchoPAC PC, GE Healthcare, UK) after the examination. The highest-quality digital image was selected for each speckle tracking analysis (Fig. 2), and the LV endocardial surface of the end-systolic frame was traced manually. The speckle tracking width was modified so as to cover the whole LV wall thickness to obtain a so-called ‘global’ strain rate curve. From that curve in the longitudinal direction, the peak early-diastolic longitudinal strain rate (GSR_E, s\(^{-1}\)) was measured as an index to directly reflect LV myocardial diastolic function.\(^{23,24}\)

Statistical Analysis

The statistical analysis was performed using standard statistical software (Dr. SPSS II for Windows, SPSS Inc., Chicago, IL, USA). All numerical data are presented as
means ± SD. Relationships between two parameters were assessed by linear correlation and regression analysis. A stepwise multiple regressions analysis was performed to find the independent determinants of global LV diastolic function among multiple parameters. A p-value < 0.05 was considered significant.

RESULTS

Clinical and echocardiographic features of the study subjects
As summarized in Table 1, the ASA values of our study subjects ranged from 95° to 158° (134° ± 13°). The E values ranged from 0.42 to 1.22 (0.80 ± 0.19) m/s, the E/A values from 0.56 to 4.15 (1.47 ± 0.64) and the IRT values from 44 to 129 (77 ± 15) msec, showing that some portion of the subjects had LV diastolic dysfunction. The ASA was significantly negatively correlated with age (r = −0.64, p < 0.001), BMI (r = −0.38, p = 0.001) and LVMI (r = −0.29, p = 0.009).

Relationship between ASA and age with GSR_E
ASA was significantly and well correlated with GSR_E (r = 0.63, p < 0.001) (Fig. 3). As shown in Table 2, the subjects’ age, BMI and LVMI were also significantly correlated with GSR_E (r = −0.49, p < 0.001, r = −0.50, p < 0.001 and r = −0.41, p < 0.001, respectively), but each correlation was relatively weaker than that between ASA and GSR_E. The stepwise multivariate analysis among ASA, age, BMI and LVMI revealed that ASA and BMI were independent predictors of GSR_E (Table 3).

Relationship between GSR_E with LV diastolic function
As illustrated in Figure 4, GSR\textsubscript{E} was significantly and well correlated with E (r = 0.68, p < 0.001). GSR\textsubscript{E} was also significantly correlated with e\textsuperscript{'} (r = 0.58, p < 0.001), IRT (r = −0.46, p < 0.001) and E/A (r = 0.53, p < 0.001), but not with DT.

**Relationship between ASA and age with LV diastolic function**

Tables 4 and 5 provided the data regarding the relationship between ASA and age with the conventional indexes of LV diastolic function. ASA was significantly correlated with E (r = 0.54, p < 0.001), e\textsuperscript{'} (r = 0.57, p < 0.001), IRT (r = −0.41, p < 0.001) and E/A (r = 0.60, p < 0.001), but not with DT. Age was also significantly correlated with E (r = −0.45, p < 0.001), e\textsuperscript{'} (r = −0.59, p < 0.001), IRT (r = 0.40, p < 0.001), E/A (r = −0.64, p < 0.001) and DT (r = 0.27, p = 0.017) (Table 5). The stepwise multivariate analysis among ASA, age, BMI, and LVMI demonstrated that (1) ASA and BMI were independent predictors for E, (2) IRT, ASA, age and BMI were independent predictors for e\textsuperscript{'} , and (3) age and BMI were independent predictors for E/A.

**DISCUSSION**

In the present study, the subjects' ASA correlated more closely with GSR\textsubscript{E}, E, and e\textsuperscript{'} than their age. The stepwise multiple regression analysis revealed that ASA and BMI, but not age, were the significant independent determinants of the GSR\textsubscript{E} and E. These results suggest that LV deformation, represented by reduced ASA, is one of the significant causes of LV diastolic dysfunction—especially of early-diastolic myocardial relaxation abnormality in otherwise healthy subjects. An extreme decrease
in ASA can cause an intense deformation of the interventricular septum, the so-called "sigmoid septum"\textsuperscript{16-20}, and LV outflow tract (LVOT) obstruction\textsuperscript{20,25-27} However, none of our 77 subjects had such an advanced deformation or LVOT obstruction. Our results primarily show the pathological role of such a minor deformation of LV shape which, thus far, has been ignored or considered merely an innocent senile change.

It has been reported that ascending aortic elongation progresses with advancing age and atherosclerosis\textsuperscript{28,29} but sufficient evidence of this has not been documented. Redheuil et al.\textsuperscript{30} and Sugawara et al.\textsuperscript{31} reported the relationship between aging and aortic elongation using magnetic resonance imaging. A decrease in the ASA is a finding frequently seen in elderly subjects, and several investigators have proposed that the ascending aortic elongation compresses the LV, causing a decrease in the ASA and deformation of the interventricular septum\textsuperscript{16-18}. If this is correct, the LV should also be compressed by the diaphragm on the side opposite to the ascending aorta. Thus, not only the interventricular septum but also the entire LV myocardium should be compressed and deformed. These considerations may explain the relatively strong relationship between the ASA and the parameters of LV diastolic function seen in the present study.

LV diastolic dysfunction is often observed in healthy older subjects. It has been suggested that age-related diastolic dysfunction may be caused by impaired active relaxation associated with abnormal Ca\textsuperscript{2+}-handling or reduced Ca\textsuperscript{2+} reuptake, and it may also be caused by impaired passive relaxation associated with myocardial viscoelasticity due to increased myocardial collagen and collagen cross-linking\textsuperscript{2,11,12}. Additionally, increased collagen and fibrous tissue in aged myocardium\textsuperscript{12-15} may
contribute to an increase in chamber stiffness, which is also an integral element of LV diastolic dysfunction. LV hypertrophy or concentric remodeling was reported to be observed in older subjects without hypertension or any other cardiovascular diseases,\(^{32-34}\) and may also play a role in the development of diastolic dysfunction in the elderly. In addition, some reports suggested that age-related loss of peripheral vascular elasticity may be associated with the deterioration of LV diastolic function.\(^{35,36}\) However, the exact mechanisms of age-related LV diastolic dysfunction are not yet clear.

In the present study, BMI was also identified as an independent determinant of LV diastolic function by multivariate analysis. It is known that LV mass can increase with obesity\(^ {37}\) and with aging even in healthy populations\(^ {32,33}\), and increased LV mass has been reported to cause LV diastolic dysfunction.\(^ {38,39}\) In the present study, LVMI was significantly correlated with GSR\(_E\), E, and E/A. However, these correlations were generally weak, and LVMI was not an independent determinant of LV diastolic function by the multivariate analysis. Therefore, although left ventricular hypertrophy might be associated with LV diastolic function, its influence might not be major in our study subjects. On the other hand, an increase in BMI is often associated with a diaphragmatic elevation, which may, in turn, compress the heart upward from the bottom. Thus, increased BMI may contribute to LV deformation and diastolic dysfunction.

There are some limitations to be acknowledged in the present study. First, the number of study subjects was limited mainly because we recruited subjects without cardiac or systemic diseases that can cause LV diastolic dysfunction such as hypertension,
diabetes mellitus, etc. As a result, our study subjects were not so old and did not include subjects with advanced septal deformation or typical "sigmoid septum." A study of subjects with more advanced LV deformation would have shown a clearer relationship between ASA, and LV diastolic function. Secondly, although a relationship between systemic arterial stiffness and LV diastolic dysfunction has been suggested, we could not assess the relationships among arterial stiffness, ASA, and LV diastolic dysfunction in this study. Further research is needed to clarify these relationships.
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FIGURE LEGENDS

Fig. 1. Measurement of the aorto-septal angle.
The angle between the right ventricular surface of the interventricular septum and the anterior wall of the aorta, i.e., the aorto-septal angle (ASA), was measured from the parasternal long-axis view at end-diastole. An example of the image with wide ASA (141°) obtained from a 52-year-old man (left panel) and that with narrower ASA (95°) from a 54-year-old woman (right panel) are shown.

Fig. 2. Measurement of the myocardial strain rate using two-dimensional speckle tracking imaging.
A region of interest (ROI) for the speckle tracking analysis was set on the entire left ventricular myocardium in the apical long-axis view (left panel). The peak early-diastolic myocardial global strain rate (GSR_E) was measured (right panel).

Fig. 3. Correlations between aorto-septal angle, age and body mass index with peak early-diastolic myocardial global strain rate from 77 subjects.
ASA, aorto-septal angle; BMI, body mass index; GSR_E, peak early-diastolic global longitudinal strain rate.

Fig. 4. Correlations between peak early-diastolic transmitial flow velocity, peak early-diastolic mitral annular velocity and left ventricular isovolumic relaxation time with peak early-diastolic myocardial global strain rate from 77 subjects.
E, peak early-diastolic transmitial flow velocity; e’, peak early-diastolic mitral annulus velocity at the interventricular septum; GSR_E, peak early-diastolic longitudinal global
strain rate; IRT, LV isovolumic relaxation time.
**Table 1. Clinical characteristics and echocardiographic features**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD (n=77)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>43.2 ± 13.8</td>
<td>20–67</td>
</tr>
<tr>
<td>Aorto-septal angle (°)</td>
<td>134 ± 13</td>
<td>95–158</td>
</tr>
<tr>
<td>Body surface area (cm$^2$)</td>
<td>1.66 ± 0.18</td>
<td>1.35–2.10</td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td>22.1 ± 2.7</td>
<td>16.8–28.4</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>65.1 ± 11.8</td>
<td>43–104</td>
</tr>
<tr>
<td>LV end-diastolic dimension (mm)</td>
<td>47.0 ± 3.7</td>
<td>38–55</td>
</tr>
<tr>
<td>LV end-systolic dimension (mm)</td>
<td>29.1 ± 3.4</td>
<td>19–39</td>
</tr>
<tr>
<td>LA end-systolic dimension (mm)</td>
<td>33.6 ± 4.6</td>
<td>23–44</td>
</tr>
<tr>
<td>Interventricular septal thickness (mm)</td>
<td>8.9 ± 1.2</td>
<td>6–11</td>
</tr>
<tr>
<td>LV posterior wall thickness (mm)</td>
<td>8.5 ± 1.1</td>
<td>6–10</td>
</tr>
<tr>
<td>LV mass index (g/m$^2$)</td>
<td>83.4 ± 15.6</td>
<td>53–115</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>65.2 ± 5.0</td>
<td>55–77</td>
</tr>
<tr>
<td>E (m/s)</td>
<td>0.80 ± 0.19</td>
<td>0.42–1.22</td>
</tr>
<tr>
<td>E/A</td>
<td>1.47 ± 0.64</td>
<td>0.56–4.15</td>
</tr>
<tr>
<td>DT (msec)</td>
<td>207 ± 45</td>
<td>107–423</td>
</tr>
<tr>
<td>IRT (msec)</td>
<td>76.5 ± 15.3</td>
<td>44–129</td>
</tr>
<tr>
<td>e′ (cm/s)</td>
<td>11.3 ± 3.2</td>
<td>5.2–17.3</td>
</tr>
<tr>
<td>E/e′</td>
<td>7.4 ± 2.1</td>
<td>3.9–14.0</td>
</tr>
<tr>
<td>$GSR_E$ (s$^{-1}$)</td>
<td>1.33 ± 0.32</td>
<td>0.62–2.17</td>
</tr>
</tbody>
</table>

DT, deceleration time of early-diastolic transmitral flow velocity; E, peak early-diastolic transmitral flow velocity; e′, peak early-diastolic mitral annulus velocity at the interventricular septum; E/A, ratio of E to peak late-diastolic transmitral flow velocity; $GSR_E$, peak early-diastolic longitudinal global strain rate;
IRT, left ventricular isovolumic relaxation time; LV, left ventricle
Table 2. Correlations between clinical and echocardiographic variables with GSR$_E$.

<table>
<thead>
<tr>
<th>Variable</th>
<th>R</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>−0.49</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>−0.50</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LV end-diastolic dimension</td>
<td>−0.17</td>
<td>n.s.</td>
</tr>
<tr>
<td>LV end-systolic dimension</td>
<td>−0.09</td>
<td>n.s.</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>−0.06</td>
<td>n.s.</td>
</tr>
<tr>
<td>LV mass index</td>
<td>−0.41</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Aorto-septal angle</td>
<td>0.63</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Abbreviations are as in Table 1.
Table 3. Stepwise multiple regression analysis for the predictors of GSR_E.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard coefficient (β)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aorto-septal angle</td>
<td>0.508</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Body mass Index</td>
<td>-0.309</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Corrected $R^2$ was 0.459, $p < 0.001$ for the model.
Explanatory variables: Aorto-septal angle, Age, Body mass index, and LV mass index.
Table 4. Correlations between clinical and echocardiographic variables with LV diastolic function.

<table>
<thead>
<tr>
<th>Variable</th>
<th>E</th>
<th>E/A</th>
<th>DT</th>
<th>IRT</th>
<th>e'</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>p-value</td>
<td>R</td>
<td>p-value</td>
<td>R</td>
</tr>
<tr>
<td>Age</td>
<td>−0.45</td>
<td>&lt; 0.001</td>
<td>−0.64</td>
<td>&lt; 0.001</td>
<td>0.27</td>
</tr>
<tr>
<td>Aorto-septal angle</td>
<td>0.54</td>
<td>&lt; 0.001</td>
<td>0.60</td>
<td>&lt; 0.001</td>
<td>−0.07</td>
</tr>
<tr>
<td>Body mass index</td>
<td>−0.39</td>
<td>&lt; 0.001</td>
<td>−0.45</td>
<td>&lt; 0.001</td>
<td>0.14</td>
</tr>
<tr>
<td>LV mass index</td>
<td>−0.27</td>
<td>0.017</td>
<td>−0.34</td>
<td>0.002</td>
<td>−0.05</td>
</tr>
<tr>
<td>LV end-diastolic dimension</td>
<td>−0.12</td>
<td>n.s.</td>
<td>−0.03</td>
<td>n.s.</td>
<td>−0.17</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>0.22</td>
<td>n.s.</td>
<td>0.11</td>
<td>n.s.</td>
<td>−0.14</td>
</tr>
<tr>
<td>GSR_E</td>
<td>0.68</td>
<td>&lt; 0.001</td>
<td>0.53</td>
<td>&lt; 0.001</td>
<td>−0.14</td>
</tr>
</tbody>
</table>

Abbreviations are as in Table 1.
Table 5. Stepwise multivariate analysis for the predictors of LV diastolic function.

<table>
<thead>
<tr>
<th>Variables</th>
<th>E</th>
<th>E/A</th>
<th>DT</th>
<th>IRT</th>
<th>e'</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>p-value</td>
<td>β</td>
<td>p-value</td>
<td>β</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td>-0.56</td>
<td>&lt; 0.001</td>
<td>0.27</td>
</tr>
<tr>
<td>Aorto-septal angle</td>
<td>0.45</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
<td>-0.34</td>
</tr>
<tr>
<td>Body mass index</td>
<td>-0.22</td>
<td>0.038</td>
<td>-0.33</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>LV mass index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Corrected R² were 0.310, p<0.001 for E, 0.493, p<0.001 for E/A, 0.074, p=0.017 for DT, 0.212, p<0.001 for IRT and 0.450, p<0.001 for e’. Explanatory variables: Aorto-septal angle, Age, Body mass index, and LV mass index. Abbreviations are as in Table 1.
Figure 2

[Image description: A Figure 2 image showing a graph and an ultrasound image. The graph displays data over a time frame, while the ultrasound image shows a cross-sectional view of a biological structure.]
Figure 3

- **GSR\(_E\) (s\(^{-1}\)) vs. ASA (degree)**: 
  - \(n = 77\)
  - \(r = 0.63\)
  - \(p < 0.001\)

- **GSR\(_E\) (s\(^{-1}\)) vs. Age (years)**: 
  - \(n = 77\)
  - \(r = -0.49\)
  - \(p < 0.001\)

- **GSR\(_E\) (s\(^{-1}\)) vs. BMI (kg/m\(^2\))**: 
  - \(n = 77\)
  - \(r = -0.50\)
  - \(p < 0.001\)
Figure 4

- **E (m/s)**: $n = 77$, $r = 0.68$, $p < 0.001$
- **e' (cm/s)**: $n = 77$, $r = 0.58$, $p < 0.001$
- **IRT (msec)**: $n = 77$, $r = -0.46$, $p < 0.001$