Age and body surface area dependency of mitral valve and papillary apparatus parameters: assessment by real-time three-dimensional echocardiography

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Aims Real-time three-dimensional echocardiography (RT3DE) has been used to quantify mitral valve (MV) annular size and leaflet tenting parameters in small numbers of patients with different pathologies. We sought to establish normal values for RT3DE mitral annular, tenting, and papillary muscle parameters over a wide age range and to study their age and body surface area (BSA) dependency.

Methods and results Transthoracic wide-angled RT3DE images of the MV were acquired in 120 subjects (52 females, 68 males, age: 37 ± 20 years) with normal left ventricular (LV) function, no risk factors, and less than or equal to mild mitral regurgitation. Custom software (RealView®) was used to trace the MV annulus, leaflets, and the papillary apparatus in mid-systole in 18 sequential cut planes obtained from the 3D data sets. Mitral valve annular area and height as well as tenting parameters (maximum and mean tenting height and mid-systolic tenting volume) were obtained and correlated with age and BSA. Wide inter-subject variability was noted in all parameters. Despite this variability, parameters directly affected by LV size were found to be BSA-dependent: MV annular area showed highest correlation with BSA ($r = 0.78$), followed by inter-papillary distance ($r = 0.58$) and postero-medial (PM) and antero-lateral (AL) papillary muscle annular distance ($r = 0.57$ and $r = 0.46$, respectively). Age did not correlate with either annular or tenting parameters, but showed moderate negative correlation with inter-papillary muscle angle ($r = -0.52$) and mild negative correlation with inter-papillary distance ($r = -0.32$), both normalized by BSA.

Conclusions Real-time three-dimensional echocardiography-derived MV annular, tenting, and papillary muscle parameters vary widely in normal subjects. When used clinically, normal values of parameters that are age- and/or BSA-dependent need to be adjusted accordingly.

KEYWORDS
Mitral valve; Papillary muscles; Echocardiography

Echocardiography has contributed significantly to the understanding of normal and abnormal mitral valve (MV) physiology.¹⁻³ This is despite the fact that assessment of the MV apparatus using two-dimensional (2D) echocardiography is difficult and experience-dependent because it requires mental integration of multiple imaging planes.⁴ To overcome these limitations, three-dimensional (3D) echocardiography, based on techniques, such as magnetic or acoustic tracking and gated sequential acquisition, has been used to improve the visualization of the mitral apparatus and quantify MV orifice size.⁵⁻⁹ However, 3D echocardiography has not been routinely used in clinical practice because previous techniques required offline reconstruction and lengthy data analysis.⁹

More recently, transthoracic real-time three-dimensional echocardiography (RT3DE) was used to quantify MV annular size and leaflet parameters in small numbers of patients with MV prolapse, ischaemic and dilated cardiomyopathy, mitral stenosis, and bioprosthetic valves.⁴,¹⁰⁻¹⁵ The main advantage of this methodology is the rapid image acquisition and fast quantification. Despite the relatively large number of published studies, there are no established RT3DE-derived normal reference values for the mitral apparatus geometry. Moreover, the relationship between such normal values and age and/or body habitus remains unknown. Accordingly, we sought: (i) to establish RT3DE-derived normal values of the mitral annulus, leaflet parameters, and papillary muscle...
length and position over a wide range of ages and (ii) to determine whether these parameters are age- and body surface area (BSA)-dependent.

Methods
Patient population
A total of 123 subjects of both genders in a wide range of ages were prospectively screened, including 62 patients recruited at University of Chicago Hospitals and 61 patients at Kawasaki Medical School and Tane General Hospital. Inclusion criteria were: normal global and regional left ventricular (LV) function [ejection fraction ≥55% and no evidence of regional wall motion abnormalities (RWMA)], absence of risk factors for coronary artery disease, and less than or equal to mild mitral regurgitation. Prior to recruitment, all patients underwent a transthoracic 2D echocardiographic study to rule-out RWMA and valvular heart disease. All participants gave written informed consent, which was approved by the Committees for the Protection of Human Subjects in Research at each institution.

Transthoracic 3D echocardiography
A SONOS 7500 scanner (Philips, Andover, MA, USA) equipped with a fully sampled matrix array transducer (X4) was used for RT3DE acquisition from the apical window with the patient in the lateral decubitus position. Full-volume acquisition in the wide-angled mode combining four ECG-triggered wedge-shaped sub-volumes (93° × 21°) was used to obtain RT3DE data sets during a single breath-hold. Care was taken to include the entire MV apparatus with the papillary muscles in the pyramidal data set. Frame rates were 16–22 frames/s, depending on imaging depth (12–16 cm). At each participating institution, image acquisition was performed by a single experienced sonographer. The volumetric data sets were digitally stored on magneto-optical disks and then transferred into a personal computer for offline analysis.

Quantification of mitral valve and papillary muscle parameters
Custom software (RealView®, YD, Nara, Japan) was used to analyse the volumetric data sets. Initially, mid-systole was identified and the anterior-posterior (AP) as well as the medial-lateral (ML) plane of the mitral annulus initialized on the respective cut planes selected from 18 sequential planes spaced 10° apart (Figure 1A and B). Subsequently, the surfaces were manually traced in each plane and the papillary muscles were identified by first initializing the mid-portion of the anterior mitral annulus at the aortic root level, followed by the postero-medial (PM) and antero-lateral (AL) papillary muscle tips (Figure 1C). Anatomical 3D images of the mitral annulus and leaflets, as well as the papillary muscles, were then automatically reconstructed in the 3D space (Figure 1D).

From these 3D images, several parameters of MV shape were calculated (Figure 1D), including: (i) MV annular area, (ii) MV annular circumference, (iii) MV annular diameter (AP and ML), and (iv) MV annular height (Figure 1D, left), with the latter used as a
Statistical analysis

Statistical analysis was performed using Microsoft Excel. Data were expressed as mean ± SD. For each measured parameter, the relationship with age, BSA, and height was calculated using the Pearson correlation coefficient. In addition, to assess the reproducibility of mitral apparatus quantification, analysis was repeated in 15 randomly selected patients 1 month later by the same observer who was blinded to the results of any previous measurements. For each parameter, intra-observer variability was calculated as the absolute difference between the two readings, in per cent of their mean, and averaged over the 15 patients. In addition, coefficient of variation was calculated for each parameter as the SD of the differences between repeated measurements in per cent of their mean.

Results

Of the initial 123 patients studied, 98% (120 patients: 52 females, 68 males, age: 37 ± 20 years, range 3–85 years, BSA: 1.68 ± 0.33 m², range 0.58–2.35 m²) had 3D images of the MV apparatus adequate for analysis. The papillary muscle analysis could not be performed in 29 patients (24%) due to inadequate visualization of the papillary muscle tips.

Table 1 summarizes the normal values of the mitral annular and leaflet parameters as well as papillary muscle measurements, including the correlations with age and BSA. Wide inter-subject variability was noted in all parameters, including mitral annular non-planarity, which was present in most normal subjects as reflected by annular height of 4.3 ± 2.1 mm and leaflet tenting height of 1.9 ± 1.5 mm. Mitral valve diameter in the anterior-posterior axis was 30.8 ± 4.4 mm (range: 19.9–45.4 mm), whereas in the medial-lateral dimension it was slightly larger: 35.1 ± 4.9 mm (range: 23.5–49.4 mm).

Female patients in our study were slightly younger and had lower BSA than their male counterparts (32 ± 18 vs. 40 ± 20 years and 1.57 ± 0.32 vs. 1.77 ± 0.31 m², respectively). Despite these differences, when correcting for BSA, there were no gender differences in MV leaflet and papillary muscle parameters, with the exception of annulus diameter: medial-lateral diameter/BSA: 22.23 ± 3.86 mm/m² for the males vs. 20.69 ± 3.00 mm/m² for the females (P = 0.02) and annular height/BSA: 2.29 ± 1.3 vs. 2.77 ± 1.05 mm/m², respectively (P = 0.03). When correcting for both age and BSA, there were no significant differences between female and male patients in the MV leaflet and papillary muscle parameters.

Parameters directly affected by LV size were found to be BSA-dependent. Mitral valve annular area and circumference showed the highest level of correlation with BSA (r = 0.78 and 0.81, respectively, Table 1 and Figure 2), followed by inter-papillary distance (r = 0.58), PM and AL papillary muscle annular distance (r = 0.57, 0.46, respectively, Figure 3). For most parameters, correlations with height were similar to those with BSA (Table 1). As demonstrated in Figures 2 and 3, age did not correlate with annular or tenting parameters, but showed a moderate negative correlation with inter-papillary muscle angle (r = −0.52) and with inter-papillary distance (r = −0.32), when normalized by BSA (Table 2).

Reproducibility data in terms of range of differences between repeated measurements in individual patients, intra-observer variability, and coefficients of variation are summarized in Table 3.

Discussion

In this study, we used transthoracic RT3DE imaging to evaluate multiple parameters of the MV apparatus, in a large number of subjects over a wide spectrum of ages. Several observations were made in this study, including: (i) the non-planarity of the saddle-shaped mitral annulus in mid-systole is widely variable in normal subjects over a wide range of ages, (ii) the position of the papillary muscles in 3D space

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>Range</th>
<th>Correlation w/BSA (r)</th>
<th>Correlation w/height (r)</th>
<th>Correlation with age after normalization for BSA (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV annular area (cm²)</td>
<td>8.6 ± 2.2</td>
<td>3.9–15.6</td>
<td>0.78</td>
<td>0.72</td>
<td>0.13</td>
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<tr>
<td>Mitral annular circumference (mm)</td>
<td>10.5 ± 1.4</td>
<td>7.0–14.0</td>
<td>0.81</td>
<td>0.76</td>
<td>−0.20</td>
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<tr>
<td>Mitral annular height (mm)</td>
<td>4.3 ± 2.1</td>
<td>0.5–9.4</td>
<td>0.27</td>
<td>0.32</td>
<td>0.20</td>
</tr>
<tr>
<td>Max. tenting height (mm)</td>
<td>5.3 ± 2.4</td>
<td>1.9–12.9</td>
<td>0.31</td>
<td>0.20</td>
<td>0.05</td>
</tr>
<tr>
<td>Mean tenting height (mm)</td>
<td>1.9 ± 1.5</td>
<td>−0.93–7.1</td>
<td>0.00</td>
<td>0.02</td>
<td>0.07</td>
</tr>
<tr>
<td>Mean mid-systolic tenting volume (cm³)</td>
<td>1.5 ± 0.9</td>
<td>0.2–5.5</td>
<td>0.41</td>
<td>0.31</td>
<td>0.15</td>
</tr>
<tr>
<td>Inter-papillary muscle angle (°)</td>
<td>28.0 ± 7.5</td>
<td>8.8–44.2</td>
<td>0.08</td>
<td>0.01</td>
<td>−0.52</td>
</tr>
<tr>
<td>PM papillary muscle annular distance (mm)</td>
<td>37.6 ± 7.8</td>
<td>20.2–53.9</td>
<td>0.57</td>
<td>0.58</td>
<td>−0.04</td>
</tr>
<tr>
<td>AL papillary muscle annular distance (mm)</td>
<td>35.4 ± 8.2</td>
<td>17.8–54.1</td>
<td>0.46</td>
<td>0.70</td>
<td>0.07</td>
</tr>
<tr>
<td>Inter-papillary distance (mm)</td>
<td>17.7 ± 4.8</td>
<td>5.7–37</td>
<td>0.58</td>
<td>0.51</td>
<td>−0.32</td>
</tr>
</tbody>
</table>
in relation to the MV apparatus in normal human hearts was relatively uniform irrespective of age; (iii) MV annular and papillary muscle parameters are BSA-dependent; and (iv) there were no significant gender-related differences in age- and BSA-corrected MV annulus, leaflet, and papillary muscle parameters.

In our study, RT3DE measurements of the MV apparatus were in agreement with previously reported values. As previously described, in normal subjects, the mitral annulus has a non-planar saddle shape configuration, with its lowest points located at the commissures, and its highest points near the aortic root and near the posterior LV wall. Although transthoracic 2D echocardiography can provide reasonable estimates of mitral annulus diameter in adults,\textsuperscript{16} it is difficult to quantify multiple parameters due to the complexity of the MV and sub-valvular structures.

Several studies have emphasized the importance of the precise visualization of the geometry of the MV–LV apparatus using RT3DE, particularly when trying to elucidate the aetiology of mitral regurgitation with its direct implications for MV repair.\textsuperscript{10–14} Real-time three-dimensional echocardiography is ideally suited to accurately evaluate the structure of the mitral apparatus, including the LV chamber and papillary muscle position. Using methodology similar to this study, Watanabe \textit{et al.}\textsuperscript{10} demonstrated that the MV annulus is saddle-shaped in healthy subjects and reported that mean saddle height and annular circumference were similar to those reported in our study. The saddle-shaped mitral annulus has been postulated to play an important role in minimizing peak mitral leaflet stress.\textsuperscript{17–20} This physiological concept has led to surgical strategies to restore the normal saddle shape of the mitral annulus.\textsuperscript{21–23}

\textbf{Figure 2} Correlations of mitral valve parameters with BSA and age (shown with linear regression line and 95% confidence intervals).
Figure 3  Correlations of papillary muscle parameters with BSA and age (shown with linear regression line and 95% confidence intervals).
In our study, in relatively large group of normal subjects evenly distributed over a wide range of ages (Figures 2 and 3, right columns), the mitral leaflets appeared nearly flat with minimal tenting. The mean tenting volume was higher than that previously reported in a small group of 10 normal subjects (1.5 ± 0.9 vs. 0.45 ± 0.29 cm³), possibly due to the differences in the number of patients and their age distribution. Despite the wide inter-subject variability of MV and papillary muscle parameters observed in this study, those directly affected by LV size showed a significant BSA dependency. These parameters included MV annular size, MV circumference, inter-papillary muscle distance, and PM papillary muscle annular distance. Although previous investigators have reported normal values for the geometry of the mitral annulus using multiplane transoesophageal echocardiography images in a small group of patients, 24 to our knowledge, our study is the first to report BSA-dependency of RT3DE-derived MV and papillary muscle parameters. Current reference values for MV size are based on 2D echocardiographic and Doppler measurements, assuming flat circular geometry of the MV annulus, whereas the saddle shape of the MV apparatus can be precisely measured from RT3DE images. Several parameters of the LV have been stratified by BSA and age by 2D echocardiography to establish reference values. These include chamber size, wall thickness, and aortic root size as well as atrioventricular valve orifice area. 25–29

The size of the MV annulus in children using 2D echocardiography has been shown to have a logarithmic relationship to BSA. 29 In contrast, our results using RT3DE showed a linear relationship with increasing body size in MV and papillary muscle parameters, which are also directly affected by LV size. These differences may be due to the fact that King et al. studied only children (age 1 day to 15 years), with a lower BSA range from 0.2 to 1.4 m² (median 0.45 m²). In contrast, our study group consisted of normal subjects, age 3–85 years, with a BSA range of 0.58–2.35 m². It is likely that in the higher BSA range, MV dimensions may show a more linear relationship to BSA. Similarly to our results, Poutanen et al., 30 using reconstructed 3D images obtained in children and young adults, age 2–27 years with BSA > 1.5 m², also showed a linear relationship between MV dimensions and increasing BSA. The mean ± SD ratio between the MVA/BSA in our patients was 5.1 ± 0.8 cm²/m². This ratio was similar to that reported by Poutanen et al., 30 who measured a mean MVA/BSA of 4.8–5.5 cm²/m², depending on BSA range, in their patients. In contrast to prior 2D echocardiographic studies, 28 our RT3DE study did not show a significant correlation between age and MV annular or tenting parameters, together with a negative correlation between age and inter-papillary muscle angle.

To our knowledge, this study is one of the first to assess the papillary muscle position in 3D space with RT3DE in humans. This entity is extremely important for the understanding of the 3D geometry of the entire mitral apparatus. Only a few studies have evaluated the displacement of the papillary muscles in the evaluation of mitral regurgitation.
in animals with RT3DE.\textsuperscript{31–33} Our study has shown the feasibility of papillary muscle geometry analysis in 76% of healthy children and adults.

**Limitations**

RT3DE images are often of lower quality than conventional 2D echocardiographic images. As the software used in the present study requires identification of mitral annulus, leaflets, and papillary muscles, technically inadequate RT3DE images could not be analysed. However, our data are similar to prior studies that have shown that the submitral apparatus is only visible in 70–80% of consecutive patients.\textsuperscript{15} Further improvements in imaging technology are necessary to enhance the resolution of the RT3DE images for improved visualization of the papillary muscles. In addition, the software used in this study measures the inter-papillary muscle angle. In the evaluation of ischaemic MR, it is important to evaluate the asymmetry of papillary muscle displacement, which is not possible with this technique.

The timing of measurements may affect the estimates of annular size. Studies have reported cyclic variations in mitral annular shape and area.\textsuperscript{19,34} The dimension of the mitral annulus is maximal and most eccentric at the time of normal maximal atrial volume. Similar to other RT3DE studies of the MV apparatus, we made mitral annular measurements in mid-systole.\textsuperscript{10–12} Therefore, it is important that inter-study comparisons of MV geometry take into account the timing of measurement in the cardiac cycle. Moreover, different to previous reports, our study was performed on a large group of patients with a wide range of BSA and ages, which makes direct comparisons between our findings and those of previous investigators difficult.

Despite these limitations, data presented in this paper on the geometry of the MV and papillary muscle apparatus in this large group of healthy children and adults support further use of RT3DE in adults with various heart diseases.

**Conclusions**

As echocardiographic assessment of the MV in 3D space for preoperative planning becomes increasingly quantitative, it is important to determine normal values of valve geometry over a wide range of ages. To address this need, our study was designed to provide RT3DE reference values for various components of the MV apparatus in normal subjects of different ages. Importantly, our data revealed wide inter-subject variability in normal RT3DE-derived MV annular geometry, leaflet tenting, and papillary muscle position in 3D space. Despite this variability, parameters directly affected by LV size were found to be BSA-dependent. Interestingly, age did not correlate with either annular or tenting parameters. Establishing reference values for MV and papillary muscle parameters that incorporate BSA-dependencies are especially important in the clinical setting, where RT3DE may become part of the routine echocardiographic examination and RT3DE measurements will be available for clinical decision-making.

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**References**


