Normal reference ranges for left and right atrial volume indexes and ejection fractions obtained with real-time three-dimensional echocardiography

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Aims The aim of this study was to obtain normal reference ranges and intra-observer reproducibility for left (L) and right (R) atrial (A) volume indexes (VI, corrected for body surface area) and ejection fractions (EF) with real-time three-dimensional echocardiography.

Methods and results One hundred and sixty-six participants, 79 males and 87 females, aged 29–79 years considered free from clinical and subclinical cardiovascular disease, were included. Normal ranges are defined as 95% reference values for atrial dimensions and reproducibility as coefficients of variations (CVs) for repeated measurements. Upper normal reference values were 41 mL/m² for maximum (max) LAVI and 19 mL/m² for minimum (min) LAVI. The lower normal reference value was 45% for LAEF. The respective values for RA were 47 mL/m², 20 mL/m², and 46%. The only relevant gender difference was a higher upper normal max RAVI among males vs. females. The CVs for repeated measurements were 9% for max LAVI, 8% for max RAVI, 13% for LAEF, and 14% for RAElf.

Conclusion The present study provides normal ranges for atrial dimensions and contractility with a new, fast, and reproducible technique that can be used bedside without offline analysis.

KEYWORDS
Reference values; Heart atria; Atrial function; Echocardiography; Three-dimensional

Introduction

Left atrial (LA) size is part of cardiac remodelling in a variety of cardiovascular diseases and a strong predictor of cardiovascular morbidity and mortality.1–4 As a contrast to numerous studies on the significance of LA enlargement, data on the clinical significance of right atrium (RA) enlargement are sparse. The assessment of RA enlargement is of importance, since it may occur in conditions like several pulmonary disorders, congenital heart disease, acquired valvular disease, and heart failure.

The most widely applied technique for measuring atrial size is two-dimensional echocardiography (2DE).5–7 The normal ranges for LA differ between studies and guidelines6–8 and are below those obtained with MRI.9 According to the most recent guidelines from the American Society of Echocardiography (ASE) and the European Association of Echocardiography (EAE), there is too little peer-reviewed validated literature to recommend normal RA volumetric values.6

Real-time three-dimensional echocardiography (RT3DE) may represent a more reproducible and robust method for atrial volume measurements than 2DE. The purpose of the present study was to obtain normal reference ranges for LA and RA volumes and ejection fractions (EF) with this new technique. In order to obtain quality insurance of such data, a reproducibility study of both RT3DE- and 2DE-derived measurements of both atria has been included.

Methods

Recruitment of participants

The aim was to include 15–20 males and females per age decade from 30 to 80 years, all employed (present and past) in our hospital. An invitation was sent to 250 potential participants selected according to these criteria. All had to give their informed, written consent to be appointed for a screening visit. A 2DE examination was performed at that visit, in order to exclude subclinical cardiac abnormalities such as significant valvular disease (stenosis or aortic-/mitral regurgitation >1/3), apparent abnormalities of cardiac chambers or function, or regional wall abnormalities. Reasons for exclusion at that visit were poor image quality, a body mass index >35 kg/m², hypertension (screening blood pressure >160/90 mmHg or on anti-hypertensive treatment), diabetes mellitus, symptoms or history of cardiovascular disease, thyroid or other endocrine dysfunction, anaemia, liver or kidney abnormalities (based upon
blood tests), or malignant disease. All had to be in sinus rhythm. Body surface was calculated according to the formula by Dubois and Dubois.\textsuperscript{10}

This study has been approved by the Regional Ethics Committee of South-Eastern Norway Regional Healthy Authority and Norwegian Social Science Data Services.

**Echocardiographic examinations**

They were performed with a Philips IE 33\textsuperscript{th} with 3D QLab Advanced software (version 6) installed. All recordings were done by one investigator with ample experience (J.E.O.). Harmonic RT3DE imaging was obtained with an X3-1 matrix array transducer with a 2.45 MHz transducer. The LV cavity was scanned in several 2D planes with a 3D matrix array transducer to obtain a comprehensive view of the LV and atria. Harmonic RT3DE imaging was used to measure the volume of the left atrium. The LV cavity was scanned in several 2D planes with a 3D matrix array transducer to obtain a comprehensive view of the LV and atria. Harmonic RT3DE imaging was used to measure the volume of the left atrium.

**Figure 1** Real-time three-dimensional echocardiography recordings of max (A) and min (B) left atrial volumes. (Top) Apical four-chamber view to the left and the orthogonal view to the right. (Middle) Short-axis view to the left and the three-dimensional model to the right. (Bottom) Time–volume curve with the vertical bar indicating either max or min volume.
temporal resolution of 18–22 frames/s. The participants were all in the left lateral decubitus position and had sinus rhythm. A wide-angled ‘full-volume acquisition mode’, in which four to five wedge-shaped subvolumes are obtained over four to five consecutive cardiac cycles, was used during held respiration. In order to optimize the imaging of each atrium, the acquisition of LA and RA dimensions was performed separately.

The RT3DE data sets were analysed with commercial software in the IE 33© machine (3D QLab©, Philips). The pyramidal volume data were displayed in three different cross-sections that could be modified interactively by manual shifting of vertical and horizontal lines in the two orthogonal apical and the short-axis views. In principal, focus was laid on the most optimal imaging of both atria in the four-chamber view. Since the first frame in the loop corresponded to

Figure 2  Real-time three-dimensional echocardiography recordings of max (A) and min (B) right atrial volumes with similar views as for left atrial dimensions in Figure 1.
ventricular end-diastole, initial measurements were performed in the frame with the largest atrial dimension, corresponding to ventricular end-systole, just before opening of the atrioventricular valves. Five anatomic landmarks were manually initialized for each chamber. For LA, this included two points to identify the mitral valve annulus in each of the two apical views, and one point to identify the centre of the posterior wall in either view. For RA, two points were set to identify the tricuspid annulus in the two apical views and one point for the centre of the posterior wall. Following this manual identification, the program automatically identified the endocardial surface using a deformable shell model. Then manual adjustments of the endocardial surface were performed in all examinations presented, in order to include trabeculae and to exclude atrial appendages and large veins from the cavity volumes. Then the frame with the smallest atrial dimension was selected with similar surface detection and manual editing. Atrial maximum (max) and minimum (min) volumes were obtained, and atrial EF were derived from the two volumes.

Usually, the time consumed to obtain these measurements was ~4-5 min for each atrium. Only technically satisfactory recordings, with two complete orthogonal views of each atrium, as demonstrated in Figures 1 and 2, were included in the data set presented.

Reproducibility

After completion of the main study, a reproducibility study of the RT3DE method was performed to compare the intra-observer variability with 2DE. For this study, 22 participants (9 females and 13 males, median age 53 (range 30–80) years) were picked at random. The mean interval between the two examinations was 5 days.

All RT3DE recordings were performed by the same investigator as in the main study. All edited atrial tracings from the first examination were available during the second. The 2DE examinations were performed by the same investigator as the 3D examinations. In order to obtain both intra- and inter-observer variability with this method, offline analyses of the same recordings were performed by a second investigator (E.A.). Loops from three cardiac cycles were obtained from the apical four-chamber and long-axis views of the LA, and from the apical four-chamber view of the RA. These loops were stored and analysed in EchoPAC® (GE Healthcare). Max atrial volumes were measured from an end-systolic frame immediately before atrioventricular opening and min volumes from an end-diastolic frame just before atrioventricular closure. Atrial volumes (V) were calculated with the area–length formula as follows:

\[
LAV = 0.85 \times (A1 \times A2)/L, \text{ where } A1 \text{ is the area in the four-chamber view, } A2 \text{ the area in the long-axis view, and } L \text{ the vertical axis, taken from the mean of the length in four-chamber and long-axis views, as in accordance with Messika-Zeitoun et al.}^7
\]

\[
RAV = 0.85 (A^2)/L, \text{ where } A \text{ is the area in the four-chamber view and } L \text{ the vertical long-axis, as described by DePace et al.}^12
\]

All variables used for reproducibility with 2DE represent the mean of three beats. To optimize repeated tracings, loops and tracings from the first examination were available during the second.

Statistical analysis

Paired and unpaired t-tests were used for comparison of continuous data between groups of subjects. Two-tailed P-values <0.05 were considered statistically significant. A near normal distribution was established using Kolmogorov–Smirnov test. The normal reference ranges are presented as mean ± 2 SD. Reference intervals for variables with a skewed distribution were obtained by calculating the mean ± 2 SD of log-transformed values and back-transformation of the confidence limits. Pearson’s correlation was used for analyses on relationship between atrial volumes and age. The intra-observer variability of repeated 2D echo and RT3DE measurements has been expressed as coefficient of variability (CV). The CV was calculated as SD of the differences divided by the mean of the variable under consideration. The analyses were implemented using SPSS® 16.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics and echocardiographic success rate

The clinical and laboratory findings from screening of the 166 participants are presented in Table 1. Only seven subjects were aged >70 years. During the screening echo examination, a small mitral regurgitation (≤1/3) was found in 29% of the study group, whereas 6% had a small aortic regurgitation and 3% had both. Technically satisfactory recordings according to our predefined criteria were obtained in 164 participants (99%) for LA and in 159 (96%) for RA.

Normal ranges for atrial volume indexes and ejection fractions

Data on normal ranges for atrial volumes and EF are presented in Table 2. Upper normal max LAVI was 41 mL/m^2 and upper normal min LAVI was 22 mL/m^2 for the entire study group, both values being slightly higher among males than females. Lower LAEF was 45%.

Upper normal value for max RAVI was 47 mL/m^2 for the entire group, with a higher upper reference value for males (50 mL/m^2) than females (41 mL/m^2). Upper min

| Table 1 Baseline characteristics of 166 healthy participants |
|-----------------|-----------------|-----------------|-----------------|
|                 | Males (n = 79)  | Females (n = 87) | P-values       |
| Age (years), n (%) |                  |                  |                 |
| 29–39 | 19 (24) | 20 (23) | NA              |
| 40–49 | 19 (24) | 26 (30) | NA              |
| 50–59 | 23 (29) | 23 (26) | NA              |
| 60–80 | 18 (23) | 18 (21) | NA              |
| Height (m) | 182 | 168 | <0.001         |
| Weight (kg) | 83 | 69 | <0.001         |
| Body surface area (m^2) | 2.05 (0.15) | 1.78 (0.14) | <0.001         |
| Body mass index (kg/m^2) | 25.2 (2.8) | 24.4 (3.5) | 0.13           |
| Systolic blood pressure (mmHg) | 127 | 124 | 0.26           |
| Diastolic blood pressure (mmHg) | 79 | 76 | 0.012          |
| Heart rate (min^-1) | 69 | 73 | 0.007          |
| Haemoglobin (g/dL) | 14.9 (0.9) | 13.2 (0.9) | <0.001         |
| Total cholesterol (mmol/L) | 5.0 (4.6–5.6) | 5.0 (4.4–5.8) | 0.63           |
| High-density lipoprotein (mmol/L) | 1.3 (1.1–1.4) | 1.6 (1.4–1.8) | <0.001         |
| Glucose (mmol/L) | 5.1 (4.8–5.5) | 4.9 (4.6–5.2) | 0.001          |
| HbA1C (%) | 5.3 (5.0–5.6) | 5.3 (5.1–5.4) | 0.31           |
| Creatinine (μmol/L) | 80 (73–88) | 65 (60–72) | <0.001         |
| Alanine aminotransferase (U/L) | 27 (21–35) | 20 (16–23) | <0.001         |

Categorical data are presented as n (%). Continuous data are presented as mean (SD) or median (25th–75th percentile).
RAVI was 20 mL/m² and was higher among males than females (22 vs. 18 mL/m², respectively). Lower RAEF was 46%. Compared with LA dimensions, the only difference was a higher upper normal level of max RAVI than max LAVI among males.

Correlations with age
Minimum LAVI had a weak positive correlation with age (r = 0.28, P < 0.001), whereas LAEF was negatively correlated with age (r = −0.25, P < 0.001). There were no statistically significant correlations between age and any of the other atrial variables.

Reproducibility
With RT3DE, the best reproducibility was found for max atrial dimensions, followed by atrial EF, whereas a poor reproducibility was noted for min atrial dimensions (Table 3). Intra-observer variability with 2DE was within the same range as RT3DE for LA, but clearly inferior for RA measurements (Table 3). The inter-observer variability was in the same range as the intra-observer variability for LA, but better for RA measurements.

Discussion
The introduction of RT3DE with fast measurements of atrial volumes and contractility requires a clinically applicable database for normality. The present study has provided such data in a relatively large cohort of carefully screened normal persons with a rather wide age range and even gender distribution. The upper normal value for RAVI max was in the range of 15% higher than for upper normal LAVI max, whereas the normal ranges of other variables were similar for both atria. Compared with time-consuming 2DE measurements, with manual tracings of three beats per variable, the new technique had a similar reproducibility for repeated LA measurements, but was superior for repeated RA measurements. Both atria could be measured successfully in most participants.

For some reason, most studies and guidelines have focused upon normal reference range of max LA dimension only. As stated by Abhayaratna et al.,1 the LA mechanical function can be described broadly by three phases within the cardiac cycle: (i) the ‘reservoir’ function during left ventricular (LV) systole which reflects the max dimension; (ii) the ‘conduit’ function during early ventricular diastole for transfer of blood into the ventricle, and through which blood flows passively from the pulmonary veins into the LV; and (iii) the ‘contractile’ function of the LA which normally serves to augment the LV stroke volume by ~20%. This relative contribution becomes more dominant in the setting of ventricular dysfunction.15,16 The end of this phase is represented by min LAV and, accordingly, LAEF. Although not extensively studied, it seems probable that these three phases are identical in RA mechanical function. Therefore, we found it natural to present normal reference ranges for max and min atrial dimensions as well as EF for both atria.

In guidelines and most studies, focus has been laid on max atrial dimensions and min EF. Various pathological conditions tend to induce an increase in atrial dimensions, with accompanying reductions in contractility. This has recently been observed in the RT3DE study by Murata et al.,17 where LA was dilated, and LAEF lower in subjects with LV diastolic dysfunction. Since LAEF correlated best with E/E’ in that study, the authors suggested that the optimal LAEF threshold for predicting an increase in LV filling pressure might be 30%, emphasizing the need for normal reference ranges not only for max atrial dimensions.

In general, the influence of gender played a minor role for the normal reference ranges for atrial volume indexes. Therefore, gender-related reference values are not deemed necessary, provided body surface area-corrected

### Table 2

<table>
<thead>
<tr>
<th>RT3DE</th>
<th>Males (n = 75)</th>
<th>Females (n = 84)</th>
<th>Total study group (n = 159)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAVI max (mL/m²)</td>
<td>15 – 42</td>
<td>15 – 39</td>
<td>15 – 41</td>
</tr>
<tr>
<td>LAVI min (mL/m²)</td>
<td>6 – 20</td>
<td>5 – 18</td>
<td>5 – 19</td>
</tr>
<tr>
<td>LAEF (%)</td>
<td>46 – 77</td>
<td>44 – 80</td>
<td>45 – 79</td>
</tr>
<tr>
<td>RAVI max (mL/m²)</td>
<td>18 – 50</td>
<td>17 – 41</td>
<td>18 – 47</td>
</tr>
<tr>
<td>RAVI min (mL/m²)</td>
<td>7 – 22</td>
<td>5 – 18</td>
<td>5 – 20</td>
</tr>
<tr>
<td>RAEF (%)</td>
<td>46 – 74</td>
<td>48 – 83</td>
<td>46 – 80</td>
</tr>
</tbody>
</table>

*Analysis based on logarithmic transformation with back transformation of the confidence limits.

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>2DE Intra-observer</th>
<th>2DE Inter-observer</th>
<th>RT3DE Intra-observer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Examiner 1</td>
<td>Examiner 2</td>
<td>Examination 1</td>
</tr>
<tr>
<td>Max LAV</td>
<td>13%</td>
<td>8%</td>
<td>12%</td>
</tr>
<tr>
<td>Min LAV</td>
<td>22%</td>
<td>23%</td>
<td>28%</td>
</tr>
<tr>
<td>LAEF</td>
<td>11%</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>Max RAV</td>
<td>14%</td>
<td>14%</td>
<td>10%</td>
</tr>
<tr>
<td>Min RAV</td>
<td>24%</td>
<td>31%</td>
<td>14%</td>
</tr>
<tr>
<td>RAEF</td>
<td>18%</td>
<td>23%</td>
<td>13%</td>
</tr>
</tbody>
</table>
variables are used. The only exception was the upper limit for max RAVI, which was 20% higher among males than females.

The influence of age was minor in this study, so that age-corrected reference ranges do not seem to be justified. Possibly, such correlations would have been stronger if more subjects <30 and >70 years had been included. The upper normal limit for 2DE-derived max LAV is 40 mL/m² in recent European guidelines on the diagnosis of diastolic heart failure and in the study of Messika-Zeitoun et al. In that study, max LAV was identical with the biplane 2DE area–length method and electron beam computed tomography.

In the ASE/EAE guidelines, the upper normal limit for max LAVI is 34 mL/m² (mean ± 2 SD). This reference value is not only derived from population studies, but it is also based upon an estimation of risk related to chamber size, and from expert opinion. The discrepancy from our upper reference may therefore not only be related to different selection criteria of the study populations and different methodology, but also to the principles for defining normality. The problem in using normal reference values based not only on population studies, is that a narrower range due to expert opinions and risk estimations, may stigmatize otherwise healthy individuals to be regarded as patients with enlarged LA.

In a study by Wang et al., RA volume was measured from the apical four-chamber view, and the long-axis was taken as a line from the midpoint of the atroioventricular valve plane to the tip of the apex. Among 48 normal, non-athletic volunteers aged 20–66 years, the upper limit for RAVI max was 31 mL/m². This is far below the upper normal value in the present study. Possible explanations for this discrepancy are different echocardiographic equipment 24 years ago and the introduction of RT3DE vs. single-plane 2DE-derived volume measurements with the Simpsons method as practiced in that study.

Cardiographic resonance (CMR) is at present considered to be the golden standard for measuring cardiac dimensions. In the study by Hudsmith et al. comprising 108 healthy volunteers aged (38 ± 12) years, upper normal limits were 80 mL/m² for max LAVI and 37 mL/m² for min LAVI. The lower limit for LAEF was 30%, far below our lower limit, and within the level suggested to indicate increased LV filling pressure. These differences are disturbing and emphasize the need for proper reference values for the actual method applied in the clinical setting. Some of the discrepancies vs. RT3DE may be related to the use of the biplane area–length method in the CMR study which incorporated inclusion of the LA appendage.

The good reproducibility for LAV measurements with 2DE is probably related to the use of three loops in both views, and the availability of former loops during the second investigation. Such a process is time-consuming and it lasted over double the time needed for RT3DE measurements of the same variables. The superiority of RT3DE measurements of RA when compared with 2DE is most probably related to the use of the single-plane method for that chamber.

The higher upper normal values with RT3DE may reflect an underestimation to the 2DE-derived normal range, as presented in the guidelines. A slight underestimation, albeit small, was found in a study on eight mongrel dogs by Khan-kirawatana et al. The same authors compared LA size measured with four different echocardiographic methods in 141 patients and found a close agreement for LAV between the biplane Simpson’s method and conventional 3D reconstruction. Badano et al. observed close correlations and narrow confidence intervals between 3D LAVs and both single-plane and biplane 2DE LAVs. Thus, most studies on reference values do not indicate a systematic underestimation of 2DE-derived LAVs when compared with RT3DE.

Study limitations

The RT3DE reproducibility study did not include inter-observer variability since we had given priority to perform these measurements by one experienced investigator. The importance of using measurements by an experienced investigator has been verified in the recent study by Mor-Avi et al., in which the bias of LV volume measurements with RT3DE vs. CMR was smaller among investigators with the highest experience. We do not have a comparator (‘golden standard’) for the atrial volumes obtained in this study. Hence, there is a possibility for a systematic bias. It cannot be excluded that some of these participants might have had asymptomatic diastolic dysfunction, since abnormal transmittal flow was not systematically recorded during screening. According to recent guidelines on the diagnosis of diastolic LV function, however, the use of blood flow Doppler measures are no longer recommended as a first-line diagnostic approach to diastolic dysfunction. The relatively poor temporal resolution of 3DE vs. 2DE, and especially M-mode echocardiography, may represent a potential issue for the functional normal range presented. The current temporal resolution is quite high, with 18–22 frames/s. All recordings were done in breath-held respiration with a regular heart rhythm. Care was taken to use the largest and smallest visualized atrial dimension for the measurements presented, as depicted in Figures 1 and 2. Therefore, we think that this problem is of minor magnitude for the volume data presented.

Conclusion

The present study has provided normal ranges for atrial volumes and EF with RT3DE from a comprehensive series of normal individuals aged 30–80 years. Upper normal values for LA volumes and EF were similar for both genders, whereas upper normal max RAVI was higher among males than females. For the total study group, max RAVI was 15% higher than max LAVI, and the remaining variables were similar for both atria. In a separate reproducibility study in 22 individuals, the reproducibility for repeated measurements of LA volumes and EF was similar with RT3DE and the 2DE biplane method with each variable representing the mean of three beats. Repeated measurements of RA with RT3DE had a superior reproducibility when compared with single-plane 2DE. The new RTDE technique is fast, fairly accurate, and reproducible and allows bedside measurements of atrial volumes and contractility.

Acknowledgements

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Conflict of interest: none declared.

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