

Effects of Age and Gender on Left Atrial Ejection Force and Volume from Real-Time Three-Dimensional Echocardiography

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Abstract

Introduction: This study was carried out to (i) provide the methodology for determining left atrial (LA) volume, emptying fraction and ejection force (LAEF), from real-time 3-dimensional echocardiography (RT3DE), and (ii) evaluate the effects of age and gender on LA volume and LAEF in a wide age range of healthy participants. **Materials and Methods:** RT3DE was performed in 102 healthy participants (age range, 20 to 80 years). From full-volume data sets, LA endocardial borders were automatically traced and LA volumes were determined. LAEF was calculated as $1/3 \times \text{mitral annular area} \times (\text{blood density}) \times (\text{peak velocity of A wave})^2$ according to Newton's law of motion and hydrodynamics; wherein the mitral annular area (MVA) is traced using RT3DE and A is the peak Doppler-derived blood velocity at atrial systole with the sample volume placed at the mitral annulus level. **Results:** ANOVA analysis revealed that LA volume indices were significantly correlated with age ($r = 0.366$, $P < 0.0001$ for maximal volume index and $r = 0.288$, $P < 0.005$ for minimal volume index). LAEF was also significantly positively correlated with age ($r = 0.49$, $P < 0.0001$). The LA emptying fraction was maintained across ages. LA volume indices and LAEF did not differ significantly with gender. **Conclusion:** Our data can be used as normal reference values for LA volumes and LAEF. We have demonstrated that age is positively related to LA volume indices and LAEF, which suggests that age-dependent cut-off values should be considered in those with heart disease.

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Key words: Age, LA Ejection Force, RT3DE, Volume

Introduction

The left atrium (LA) plays the primary role in the filling of the left ventricle (LV). A number of studies have demonstrated that LA enlargement (i.e. volume increase) is a negative prognostic factor for survival in patients with a variety of cardiovascular disorders, including stroke, congestive heart failure and myocardial infarction.¹⁻⁵ In the absence of mitral valve disease, an enlarged LA is also a marker of chronic elevated LV filling pressures.⁶ LA ejection force (LAEF) is a measure of atrial systolic function and plays an important role in LV diastolic filling. In a similar way to LA enlargement, LAEF also serves as an independent determinant of prognosis in patients with heart failure.^{7,8} Real-time 3-dimensional echocardiography (RT3DE) is a new non-invasive imaging technique that has been shown to be useful for assessing LA volumes due to

its high feasibility rate of data acquisition and convenient semi-automated offline analysis.⁹ Unfortunately, the prior methodology for LAEF determination¹⁰ has proven to be inaccurate. Also, to our knowledge, there have been no published studies on the effect of age and gender on LA volume and LAEF as assessed by RT3DE in healthy participants. Therefore, our main aims were to (i) provide the methodology for determining LA volume, emptying fraction and ejection force using RT3DE, and (ii) determine the effects of age and gender on LA volumes and LAEF using RT3DE in healthy participants across a wide range of ages. Accordingly, the outcomes would establish reference standards for future studies regarding the assessment of LA volumes and contractile function in patients with atrial fibrillation or LV diastolic dysfunction.

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Materials and Methods

Study Participants

From June 2008 through November 2009, we evaluated 137 healthy participants who underwent echocardiography. Of these, 102 had good quality echocardiographic images for LA volume assessment. The echocardiograms of these participants were studied and their data analysed. Participants included 46 males and 56 females, with age ranging from 20 to 80 years (median age: 47 years). The weight and height of all participants were recorded, and their body surface area (BSA) was calculated. Participants were divided into 5 groups according to their age: <30 years, 30 to 40 years, 41 to 50 years, 51 to 60 years, and >61 years. The study protocol was approved by the Institutional Review Board and informed consent was obtained from all participants.

Echocardiography

All participants underwent transthoracic echocardiography (IE33, Philips) according to recommended guidelines.¹¹ The transmitral flow, pulmonary venous flow and tissue Doppler imaging were recorded from a 2D apical 4-chamber view. Mitral flow was recorded at the tips of the mitral leaflets and at the level of the mitral annulus using pulse wave Doppler during quiet respiration. The peak velocity of early diastolic flow (E velocity), peak velocity of late diastolic flow (A velocity) and the E/A ratio were determined. The average value of septal and lateral E/E' indices was calculated as a marker of LV diastolic filling pressure. Pulmonary venous flow was recorded with the sample volume at 1 cm into the pulmonary vein. Peak systolic velocity (S), early diastolic velocity (D) and velocity at atrial contraction (AR) were measured, and the S/D ratio was calculated. The 2D images were obtained in standard apical 4- and 2-chamber views. All measurements were assessed at 3 consecutive beats. Each value was recorded, and the arithmetic mean was calculated.

RT3DE for LA Volume and Function

The RT3DE was acquired using an X3-1 matrix transducer on a Phillips IE33 (Phillips Medical Systems, Andover, MA). Apical full-volume images were acquired over 4 cycles. The images were aligned to obtain the optimal border delineation of the LA in the far field. The 3D longitudinal axis was aligned parallel to the LA axis. The 3D transverse axis was placed at the level of the LA where it crossed the 3D longitudinal axis approximately at the LA geometric center point (Fig. 1A). Maximum LA volume was measured in the frame just before mitral valve opening. Minimum LA volume was measured in the frame just at mitral valve closure.¹² Semi-automatic LA border tracing

Figure 1A

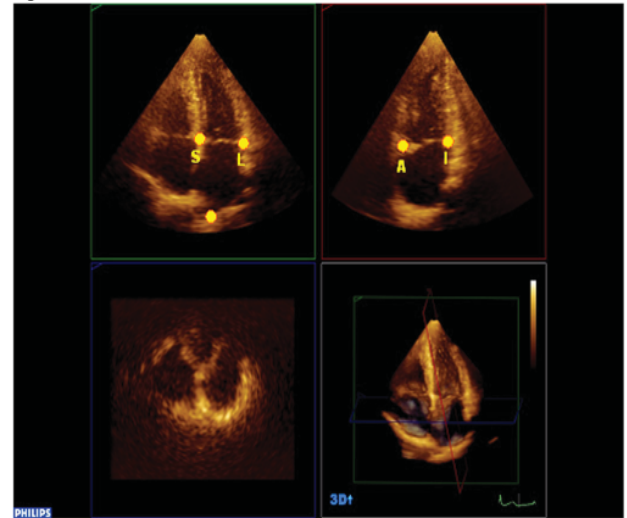


Figure 1B

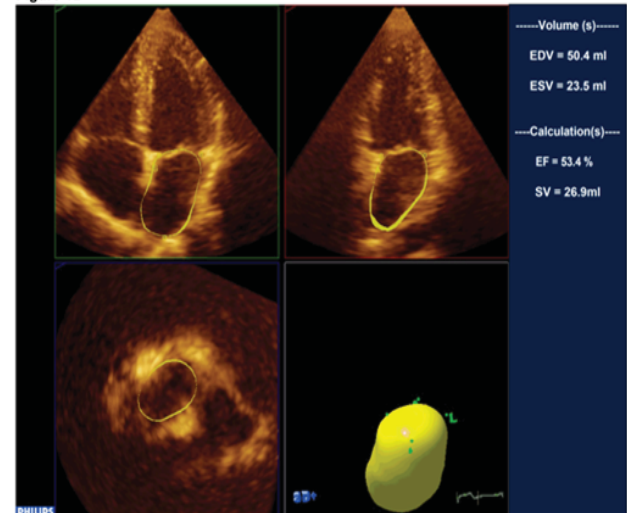


Fig. 1. From RT3DE, semi-automatic left atrial border tracing is carried out by marking (●) at 4 mitral annular points (lateral, septal, inferior, anterior) and an atrial superior dome point opposite the annulus (A). The automatic border tracing is shown by the software. The left atrial end diastolic volume (EDV), end systolic volume (ESV) and ejection fraction (EF) are calculated automatically by the software and displayed on the right side of the screen (B).

RT3DE: real-time 3-dimensional echocardiography, SV: stroke volume

was performed in LA systole and diastole by marking 4 mitral annular points (lateral, septal, inferior, anterior) and an atrial superior dome point opposite the annulus (Fig. 1A). The LA maximal and minimal volumes were automatically calculated by the software. The LA emptying fraction was calculated using the following formula: $[(\text{LA maximum volume} - \text{LA minimum volume}) / \text{LA maximum volume}] \times 100\%$ (Fig. 1B).

LAEF Determination

The LAEF has been proposed as a measure of atrial biomechanical function.¹⁰ LAEF is the force exerted by the LA to propel blood across the mitral valve into the LV during atrial systole. Based on the Newtonian principle, the LAEF is calculated as the product of the mass and acceleration of blood from the LA during atrial systole. The mass of the blood can be calculated as the product of the density of blood ($\rho = 1.06 \text{ g/cm}^3$) and the volume of blood that passes through the mitral annulus. In 1993, Manning et al¹⁰ surmised LAEF to be: $\text{LAEF} = 1/2 \times \rho \times \text{MVA} \times A^2$, where MVA is the mitral valve annulus area $[= \pi \times (\text{MVD}/2)^2]$, on the assumptions that (i) the mitral valve orifice is circular, (ii) its diameter is measured from the apical 4-chamber view, and (iii) A is the blood velocity at atrial systole (with the sample volume placed at the mitral annulus level rather than at the leaflet tips). However, the derivation of the Manning formula is not accurate.¹³

We therefore decided to derive the LAEF based on principles of hydrodynamics. Figure 2 shows the blood velocity across the mitral annulus. During atrial systole, at

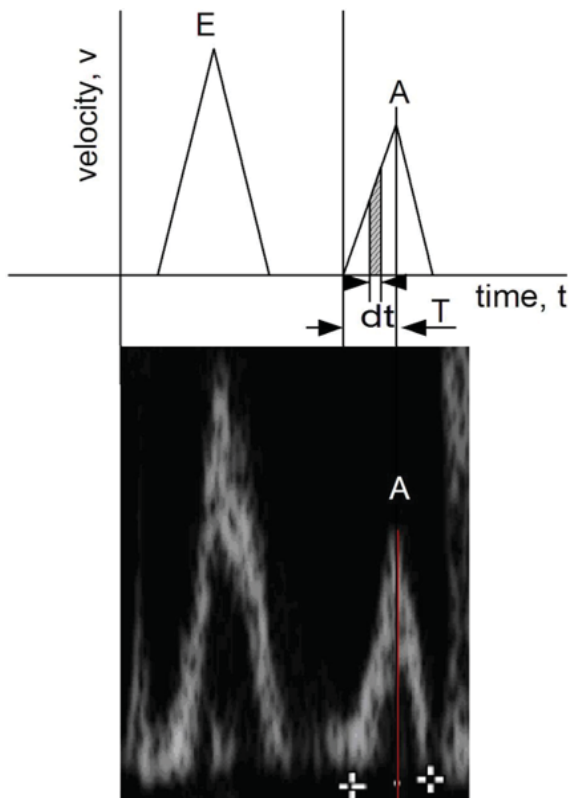


Fig. 2. Schematic drawing of trans-mitral flow (Top) and pulsed Doppler recording at mitral annulus (Bottom). The T is time to peak velocity A from a reference point at the onset of atrial systole. The instantaneous velocity v (at time t) is given by At/T , and mitral annulus area a (at time t) is given by $(MVA)t/T$.

any time t , the instantaneous blood velocity v is deemed to be given by $v = At/T$; and the mitral annulus area, a , is given by $a = (MVA)t/T$, wherein (i) T is the time to peak velocity A , and (ii) MVA is the area corresponding to peak velocity.

Blood volume exiting during time interval dt is $dV = a \times v \times dt$, and the LAEF at time t during time interval dt is equal to $m(t) \times dv/dt$. Hence, the total LAEF is:

$$\text{LAEF} = \int_0^T m(t) dv/dt \quad (1)$$

Substituting $m(t) = \rho a v dt = \rho [(MVA)t/T][At/T]dt = \rho (MVA)A(t/T)^2 dt$ and $dv/dt = A/T$ into equation (1), we obtain

$$\text{LAEF} = \frac{\rho (MVA) A^2}{T^3} \int_0^T (t^2) dt = \frac{1}{3} \rho (MVA) A^2 \quad (2)$$

Therefore, the final formula is as follows: $\text{LAEF} = 1/3 \times \rho (MVA) A^2$, where (i) ρ is the blood density (1.06 g/cm^3), (ii) MVA is the mitral annulus area corresponding to peak atrial velocity A , (iii) A is obtained by pulsed wave recording when the sample volume is placed at the mitral annulus level rather than at the leaflet tips, and (iv) the peak velocity of A waves is obtained by averaging over 3 consecutive beats. Using RT3DE, the MVA is determined by tracing the inner border of the mitral annulus. Examples of measurements employed for LAEF in young and older healthy participants are shown in Figure 3.

Inter-observer Viability Test

The results of 20 participants were randomly selected and repeat analyses were independently performed by 2 investigators who were each blinded to the other's results. The inter-observer reproducibility was assessed by calculating the mean difference and standard deviation between the results, with the percentage variability equal to the mean of the absolute values of the differences between the 2 measurements divided by their mean.

Statistical Analysis

Continuous variables are presented as mean $\pm$ SD, and dichotomous variables as number and percentage. Differences in continuous variables between groups were calculated using one-way analysis of variance (ANOVA) with post hoc Bonferroni correction. Gender differences were determined by using an independent-sample test. The relationship between continuous variables was analysed by using regression analysis and the Pearson's correlation coefficient. A P value < 0.05 defined a significant result.

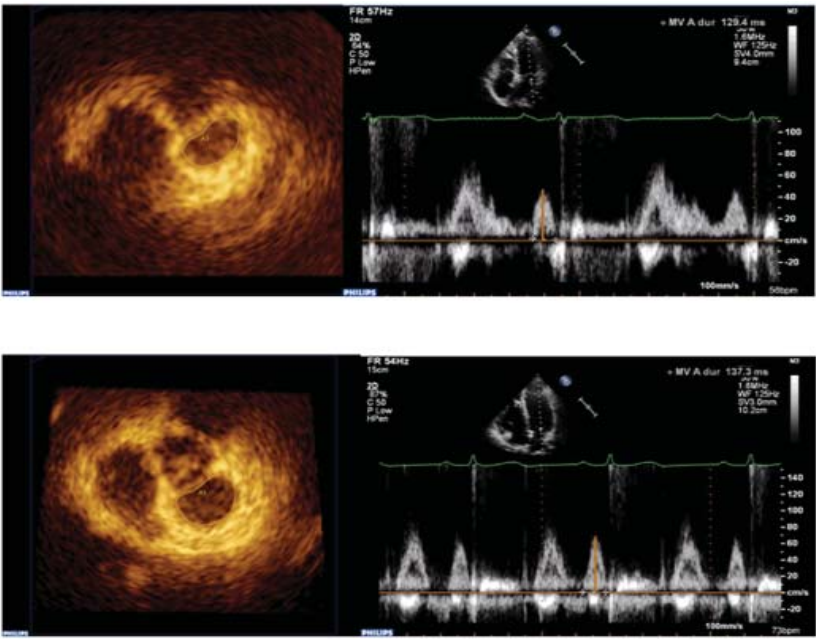


Fig. 3. Sample measurements of LA ejection force for young healthy participant (25 years old) (upper panel) and older healthy participant (63 years old) (lower panel). Mitral annulus area is measured by RT3DE (left column) and peak velocity of A wave (right column) was measured by pulsed-Doppler echocardiography. The calculated LA ejection force was 3.11 kdyne and 9.40 kdyne in the young and older participant, respectively. LA: left atrial; RT3DE: real-time 3-dimensional echocardiography

Results

Participant physical characteristics are shown in Table 1. The significant findings were a decrease in height and an increase in systolic blood pressure with increasing age.

LA volume and function from RT3DE

The data on LA volumes using RT3DE are shown in Table 2. LA volumes significantly increased with age. The LA maximal and minimal volume indices were correlated with age ($r = 0.366$, $P < 0.0001$ and $r = 0.288$, $P < 0.005$, respectively). Overall, no differences were found between men and women regarding LA maximum and minimum volume indices (Fig. 4). As noted in Table 2, the LA emptying fraction was maintained across ages. As expected, the E/A ratio declined significantly with age ($P < 0.0001$). The E/E'

and S/D ratios increased, and the pulmonary vein diastolic velocity (D) decreased significantly with age (all $P < 0.0001$). The LA maximum volume index was positively significantly associated with septal E'/A' ($r = 0.23$, $P < 0.05$), septal E/E' ($r = 0.26$, $P < 0.05$) and lateral E/E' ($r = 0.18$, $P = 0.075$) and the average of both ($r = 0.20$, $P < 0.05$).

LA Ejection Force

We found that LAEF increased significantly with age ($r = 0.49$, $P < 0.0001$) (Table 2). Overall, no differences between men and women were found in LAEF (Fig. 5). LAEF was positively associated with E/A ratio of the mitral flow ($r = 0.59$, $P < 0.0001$), septal E'/A' ($r = 0.49$, $P < 0.0001$) and E/E' ($r = 0.45$, $P < 0.0001$).

Table 1. Participant Physical Characteristics

Characteristic	<31 (n = 20)	31 to 40 (n = 22)	41 to 50 (n = 14)	51 to 60 (n = 27)	>60 (n = 19)	ANOVA P value
Male (%)	45	50	43	26	53	0.36
Weight (kg)	61 ± 13	64 ± 15	70 ± 13	61 ± 10	61 ± 9	0.18
Height (cm)	166 ± 8	166 ± 10	164 ± 9	160 ± 7	160 ± 8	0.04
BSA (m ²)	1.67 ± 0.18	1.71 ± 0.23	1.76 ± 0.19	1.63 ± 0.16	1.63 ± 0.16	0.18
HR (bpm)	74 ± 11	73 ± 10	78 ± 8	72 ± 11	75 ± 9	0.39
Systolic BP (mmHg)	118 ± 10	119 ± 14	123 ± 11	122 ± 14	130 ± 9*	0.03
Diastolic BP (mmHg)	71 ± 9	76 ± 10	76 ± 8	72 ± 8	75 ± 9	0.20

* $P < 0.05$ vs participants aged <31 years

ANOVA: analysis of variance; BP: blood pressure; bpm: beats per minute; BSA: body surface area; HR: heart rate

Table 2. Left Atrial Volume and Function, and Left Atrial Ejection Force, in Normal Participants by Age

Characteristic	<31 (n = 20)	31 – 40 (n = 22)	41 – 50 (n = 14)	51 – 60 (n = 27)	>60 (n = 19)	ANOVA P value
Maximal volume index, (mL/m ²)	19 ± 4	21 ± 4	22 ± 6	24 ± 4*	25 ± 5*	0.004
Minimum volume index, (mL/m ²)	9 ± 2	11 ± 4	10 ± 2	11 ± 3	13 ± 4*	0.022
LA emptying fraction, (%)	50 ± 9	50 ± 11	54 ± 9	54 ± 7	48 ± 9	0.21
E/A ratio	1.9 ± 0.4	1.9 ± 0.6	1.3 ± 0.4*†	1.4 ± 0.4*†	1.1 ± 0.5*†	<0.0001
DT(s)	0.20 ± 0.03	0.24 ± 0.09	0.23 ± 0.03	0.23 ± 0.02	0.25 ± 0.04	0.052
E/E' ratio	7.4 ± 1.5	7.8 ± 1.5	9.0 ± 2.3	9.9 ± 1.6*†	10.0 ± 2.2*†	<0.0001
Pulmonary vein S velocity (cm/sec)	48 ± 10	55 ± 10	54 ± 12	56 ± 12	56 ± 14	0.033
Pulmonary vein D velocity (cm/sec)	52 ± 12	53 ± 11	46 ± 10	44 ± 10*†	41 ± 8*†	0.001
Pulmonary vein AR velocity (cm/sec)	24 ± 4	25 ± 3	32 ± 18	28 ± 4*†	30 ± 7*†	0.022
S/D ratio	0.95 ± 0.28	1.05 ± 0.21	1.21 ± 0.32	1.32 ± 0.30*†	1.37 ± 0.32*†	<0.0001
LA ejection force (kdyne)	4.0 ± 1.4	4.0 ± 1.3	5.4 ± 2.2	5.2 ± 2.1	5.8 ± 2.0*†	<0.005

*P < 0.05 vs participants aged <31 years

†P < 0.05 vs participants aged 31 to 40 years

ANOVA: analysis of variance; AR: atrial reversal of flow in late diastole; D: peak diastolic velocity; DT: deceleration time; E/A: peak velocity of early diastolic flow / peak velocity of late diastolic flow; E/E': peak velocity of early diastolic flow across mitral valve / peak septal annular velocity of early diastole; LA: left atrium; S: peak systolic velocity

Inter-observer Variability

The mean inter-observer difference for maximum LA volume index was 1.05 ± 0.84 mL/m², whereas the percentage variability was $5.53 \pm 4.46\%$. The mean inter-observer difference for LAEF was 0.42 ± 0.31 kdyne, whereas the percentage variability was $6.70 \pm 3.12\%$ (Table 3). The propagation error analysis for LAEF is shown in the Appendix.

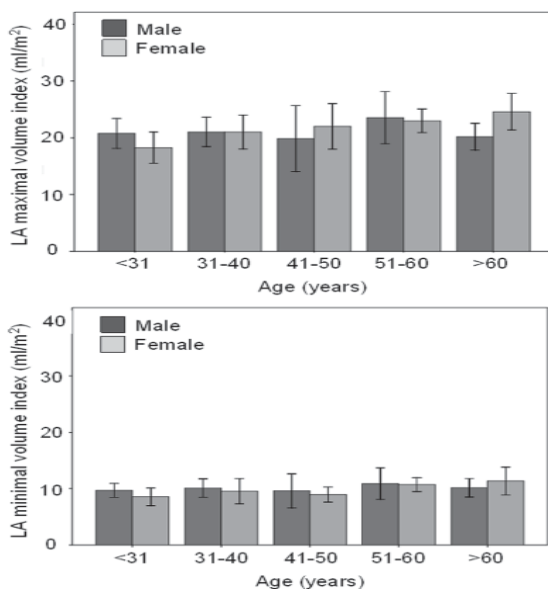


Fig. 4. Maximum and minimum LA volume indices in healthy participants across 5 age groups according to gender. Data are expressed as mean and 95% CI. LA volume increases significantly with age, but is not significantly different between males and females.

CI: confidence interval; LA: left atrial

Discussion

The main finding of our study was that age is positively associated with LA enlargement. This is likely to be a result of impaired LV diastolic function with increasing age. This is also shown by the analysis of transmitral flow patterns, detected using pulse-wave Doppler and tissue Doppler imaging, in which there is a progressive increase in LAEF in older participants. There was no effect of gender on LA volume indices or LAEF. Our population study showed age to be very strongly associated with LA volume indices and LAEF, which indicates that ageing should be considered an independent factor in the development of LV compliance abnormalities.

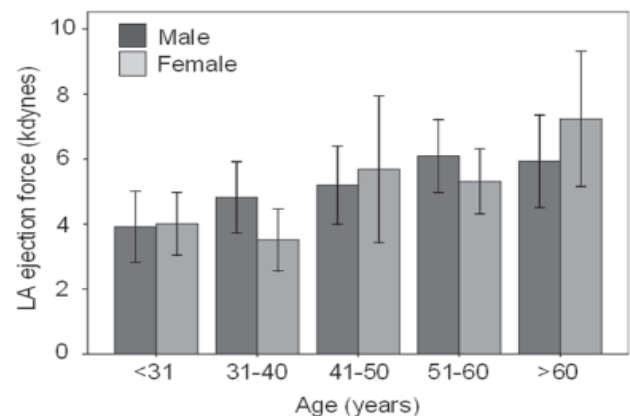


Fig. 5. LA ejection force in healthy participants across five age groups according to gender. Data are expressed as mean and 95% CI. LA ejection force increases significantly with age, but is not significantly different between males and females.

CI: confidence interval; LA: left atrial

Table 3. Inter-observer Variability for Left Atrium Volumes, Emptying Fraction and Ejection Force

Characteristic	Maximal volume index (mL/m ²)	Minimal volume index (mL/m ²)	Emptying fraction (%)	LA ejection force (kdyne)
Mean	19.9 ± 4.5	8.7 ± 2.0	56 ± 4	5.0 ± 1.8
Mean difference	1.1 ± 0.9	0.6 ± 0.4	3 ± 3	0.42 ± 0.31
% variability	5.53 ± 4.46	6.89 ± 4.71	5.01 ± 4.43	6.70 ± 3.12
Correlation coefficient	0.97	0.94	0.67	0.96
t-test <i>P</i> value	NS	NS	NS	NS

Mean, Mean difference and % variability are mean±SD

LA: left atrium; NS: not significant

LA volume determination using RT3DE

Three-dimensional echocardiography evaluation of LA volume has been shown to be accurate and to correlate well with gold standard magnetic resonance imaging (MRI). Initial work on 3D volume estimation^{14,15} was done by using the non-real-time echocardiography, which is labour intensive and time-consuming as the images had to be manually acquired using a 2D rotating transducer and then reconstructed off-line on the workstation. The images are also subjected to motion and respiratory artifact. Nevertheless, they showed good correlation with MRI estimations of LA volume ($r = 0.90$, $SEE = 9.6$ mL, $P < 0.001$). Recent work by Artang et al⁹ using RT3DE has confirmed the accuracy of 3D echocardiography for LA volume estimation compared to MRI ($r = 0.86$ for systole, $r = 0.76$ for diastole, $r = 0.88$ for ejection fraction, $P < 0.0001$ for all). Furthermore, 3D echocardiography has been shown to be more accurate in the estimation of LA volume than either M-mode or 2D echocardiography. Jenkins et al¹⁶ assessed LA volume using M-mode and 2D echocardiography methods (including area-length and Simpson's methods) in 106 patients and compared the results to measurements made using RT3DE. They showed greater test-retest variation in M-mode and 2D echocardiography estimation of LA size compared to RT3DE ($r = 0.98$, $P < 0.01$). Inter-observer agreement between measurements was best for RT3DE ($r = 0.99$, $P < 0.01$), and worst for M-mode ($r = 0.89$, $P < 0.01$).

The study by Artang et al⁹ showed that echocardiography systematically underestimates LA volumes compared to MRI. This phenomenon is based on previous comparisons of echocardiography versus MRI and gated cardiac computer tomography for assessment of LA volumes.^{14,17,18} A likely explanation is the difference in spatial image resolution between the 2 imaging techniques. In RT3DE, the apical window places the LA in the far field of the ultrasound beam,

resulting in loss of lateral image resolution. MRI enables better image resolution and thus permits more accurate border detection of the LA compared to RT3DE, which could explain the difference in volume observed between these modalities in the literature. The underestimation of LA maximal and minimal volumes by RT3DE results in mild overestimation of LAEF compared to MRI. In the present study, however, we did not perform MRI for all participants and we were therefore unable to compare LA volume variations between MRI and RT3DE measurements.

Overall, the RT3DE with semi-automatic border detection is a practical alternative for obtaining LA volume, and has been shown to have good correlation with MRI measurements.⁹ Furthermore, with RT3DE, LA volume data can be obtained at multiple time points per cardiac cycle, which is suited for studying the phasic changes in LA volumes.

LAEF Determination using RT3DE

Manning et al¹⁰ introduced the LAEF concept in 1993 and calculated it using transthoracic echocardiography with the formula $1/2 \times \rho \times MVA \times A^2$. In 2000, Tokushima et al¹⁹ derived the formula with a different coefficient "1/3" based on hydrodynamic principles, but did not provide the detailed derivation. In this study, we have systematically derived the formula for LAEF. The values of LAEF in healthy participants in our study were different from Manning's study due to the different coefficient value in the formula and the use of different methods. Our derivation provides a mathematically-based scientific insight into the basis and use of the LAEF formula. In our derivation, the mitral annulus area is obtained using RT3DE, and the mitral flow velocity A is measured by placing the sample volume at the mitral annulus position. A minor technical limitation on the use of the LAEF formula is the non-simultaneous measurements of the peak velocity A and the mitral annulus area. From the formulation, we see that the propagation error of LAEF originates from the measurement of mitral annulus area and peak velocity A . Our propagation error analysis found an error of 5.06%.

Effect of age on LA Volume, Emptying Fraction and Ejection Force

The effect of age on LA volume and function has been studied using 2D and 3D echocardiography.^{5,20-24} Spencer et al²⁴ studied LA volumes via cross-sectional acoustic quantification in a large group of healthy participants aged 3 to 79 years using 2D echocardiography. Similar 2D echocardiography studies of elderly participants (mean age: 76 years) have recently been reported.^{22,25} These studies have shown age and sex differences in LA volumes. In

vivo validation studies have found that compared to 3D echocardiography and MRI, 2D echocardiography is likely to underestimate LA volume.¹⁴ In 2003, Poutanen et al²³ reported LA volumes and function assessed using 3D echocardiography in 169 healthy children and young adults and found that LA volume indices increase with growth, with no differences between boys and girls. The major limitation of that study was the use of non-real-time 3D echocardiography, wherein LA volume was reconstructed offline. In order to overcome this problem, RT3DE (using a matrix probe) is carried out for acquisition of instantaneous volumetric images. Rapid image acquisition also decreases the risk of motion artifact.

In our current study, we found a significant correlation between LA volume and age using RT3DE. In contrast, a study by Thomas et al²⁶ showed that normal ageing did not affect atrial size. However, similar to our finding, other studies have reported age-related LA enlargement that may be a consequence of abnormal relaxation rate with age.^{5,20,21} We found no significant difference in LA volume between men and women. Greater age did not appear to affect the LA emptying fraction.

Manning et al¹⁰ was the first to report that LAEF provides a physiologic assessment of atrial systolic function. Mattioli et al²⁷ also reported that LAEF correlated with age ($r = 0.90$) in healthy participants. A similar age-dependent relationship was found in 35 healthy participants ($r = 0.74$, $P < 0.0001$) by Inoue et al¹³ and in 356 hypertensive patients ($r = 0.34$, $P < 0.001$) by Cioffi et al.²⁸ Our current study confirmed this positive correlation between LAEF and age. Our explanation is that increasing age results in impairment of LV relaxation (i.e. the LV stiffens with age), whereby filling is reduced at early diastole.²⁹ Thus, a greater LAEF is required, providing a booster that the heart needs to pump blood from the LA to ensure adequate filling of the LV. We found no significant difference in LAEF between men and women.

Limitations

First, this study was limited by a relatively small sample size, which may limit the power of statistical analysis. Second, we did not measure the LA volume at the P wave on the ECG. Thereafter, the passive and active emptying fractions of LA were not calculated. Third, there is a lack of validation of echocardiographic findings with independent methods of assessment (i.e. MRI).

Conclusion

RT3DE is well suited to the study of LA volume and LAEF. Age appears to be positively related to LA volume indices and LAEF, which suggests that age-corrected values should be considered for healthy individuals and for those

with heart disease.

Acknowledgements

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Appendix

Propagation of error analysis for LA ejection force:

For the LA ejection force $= 1/3 \times \rho \times MVA \times A^2$; where MVA is the mitral valve annulus area, ρ is blood density and A is the velocity of atrial filling.

Hence, MVA and A are two measured quantities with errors ΔMVA and ΔA , respectively. By using the Pythagorean theorem, we obtain $\Delta LAEF/LAEF = 2((\Delta MVA/MVA)^2 + (\Delta A/A)^2)^{1/2}$. Here we take the intra-observer variability as measurement errors in D and A. $\Delta MVA/MVA = 4.89\%$, $\Delta A/A = 1.32\%$, and then the error in the index $\Delta LAEF/LAEF = 5.06\%$.