Assessment of the Developmental Change in the Left Atrial Volume Using Real-Time Three-Dimensional Echocardiography

Noboru Tanaka, MD[1,2], Kiyohiro Takigiku, MD[2], Ken Takahashi, MD[1], Ayako Kuraoka, MD[2, 3], Kotoko Matsui, MD[1], Satoru Iwashima, MD[4], Masaki Nii, MD[5], Manatomo Toyono, MD[6], Masaaki Takeuchi, MD[7], Masahiko Kishiro, MD[1], Satoshi Yasukouchi, MD[2], and Toshiaki Shimizu, MD[1]

[1]Department of Pediatrics, Juntendo University Faculty of Medicine

[2]Department of Pediatric Cardiology, Nagano Children's Hospital

[3]Department of Pediatrics, Kyushu Kosei Nenkin Hospital

[4]Department of Pediatrics, Hamamatsu University Faculty of Medicine

[5] Department of Pediatric Cardiology, Shizuoka Children's Hospital

[6]Department of Pediatrics, Akita University Faculty of Medicine

[7]University of Occupational and Environmental Health, School of Medicine

Short title: Developmental change in the LA volume using RT3DE

Address for correspondence:

Kiyohiro Takigiku, MD, FJCC

Nagano Children's Hospital, Department of Pediatric Cardiology

3100 Toyoshina, Azumino City, Nagano

399-8205, Japan

Phone: +81-263-73-6700, E-mail: ktaki@naganoch.gr.jp

Abstract

Aims: Real-time 3D echocardiography (RT3DE) has been applied for the assessment of Left atrial (LA) function in patients with adult heart disease; however, LA function is not well known in children. We aimed at determining the normal range of LA volume (LAV) using RT3DE and the feasibility and reproducibility of this method in healthy subjects and at elucidating the developmental changes in the LAV with aging.

Methods and Results: In this study, 345 healthy people (mean age, 24.3 ± 21.3; range, 0.1–76.4 years) were enrolled. We performed transthoracic RT3DE and measured the maximum and minimum LAV. Simultaneously, we measured the LAV using the 2D biplane Simpson's method. Interobserver and intraobserver variability and the agreement of LAV measurements between RT3DE and 2DE were assessed in a subset of subjects. The RT3DE feasibility for LAV measurement was 93%. Both maximum and minimum LAVs exponentially increased with age and linearly increased with increasing BSA. LA distensibility decreased slightly with age and BSA. The LAVs measured by RT3DE were significantly smaller than those measured by the 2D biplane Simpson's method. The 3D volumetric method had favorable intraobserver and interobserver agreement.

Conclusion: The reference values of LAV from early infancy to adulthood were obtained using RT3DE, which could be useful for future studies in children with congenital heart disease. RT3DE is a reproducible method and a feasible tool for evaluating the LAV in children. LA reservoir function is likely to decrease with age and increasing of body size.

Key words: real-time 3D echocardiography, LA distensibility, child

Abbreviations: left atrium/atrial = LA, left atrial volume = LAV, real-time 3-dimensional echocardiography = RT3DE, two-dimensional echocardiography = 2DE, multidetector computed tomography = MDCT, magnetic resonance imaging = MRI, body surface area = BSA, intraclass correlation coefficient = ICC, left atrial volume index = LAVI, limits of agreement = LOA, left ventricle = LV, computed tomography = CT, left ventricular filling pressure = LVFP

Introduction

The left atrial (LA) size is a clinically important measure that can indicate the presence of adverse cardiovascular events[1-3]. Recently, LA volume (LAV) assessment using real-time 3-dimensional echocardiography (RT3DE) has had an impact on the diagnosis of major cardiovascular events in adults[4, 5]. However, there are no data on normal LAV using RT3DE for clinical applications in children with congenital heart disease. It is very important that the assessments of LA enlargement and function have relation to heart failure in patients with congenital heart disease. Therefore, it is necessary to determine the normal values of LAV in healthy children and to identify the developmental changes in the LAV with aging.

The use of RT3DE has been recently introduced as a new technique for the assessment LAV, and RT3DE has known to be a more reproducible and robust method for LAV measurements than two-dimensional echocardiography (2DE)[6-9]. LAV measures can be obtained more easily with 3D matrix array transducers and semi-automated computer algorithms, and LAV measures obtained with RT3DE have been shown to have a good correlation with those obtained with multidetector computed tomography (MDCT) and magnetic resonance imaging (MRI)[10-14].

Hence, the purpose of this study was to determine the normal range of LAV using

RT3DE and the feasibility and reproducibility of this method in a large population of healthy subjects and to clarify the changes of LAV and LA distensibility across the wide span of age, when comparing the difference of theses among children and adults.

Methods

Study subjects

This study included 174 healthy children (mean age, 8.2 ± 2.6 years; range, 0.1–12.0 years; 85 boys), 25 young adults (mean age, 14.7 ± 1.9 years; range, 12.0–17.9 years; 11 male young adults), and 146 adults (mean age, 45.2 ± 17.2 years; range, 18.0–76.4 years; 70 male adults) at 4 collaborating institutions. The eligibility criteria included (1) normal blood pressure and no history of hypertension at the time of examination; (2) absence of diabetes, hypercholesterolemia and/or cardiovascular disease; (3) no cardiac medications; and (4) age- and sex-based height and weight between the 25th and 75th percentiles. The subjects were recruited from hospital employees, their relatives, and volunteers. All subjects underwent a physical examination and 2-D echocardiography to exclude those with valvular disease or the presence of regional wall motion abnormalities. The ethics committee from each of the hospitals approved the study protocol, and informed consent was obtained from all of the subjects.

All individuals were submitted to comprehensive 2-dimensional echocardiographic studies according to American Society of Echocardiography guidelines and LAVs were calculated by the biplane modified Simpson's method using the apical 4 and 2 chamber view in the Xcelera workstation (Philips Medical System, Andover, MA, USA) and TomTec Cardio View Software (TomTec Inc., Chicago, IL, USA). The RT3DE dataset was obtained from each institution and sent to the core institution of Nagano Children's Hospital for analysis, and a single doctor (T. N.) retrospectively analyzed the 2DE and RT3DE data.

Real-time 3D echocardiography

We performed transthoracic RT3DE using iE-33 (Philips Medical System, Andover, MA, USA) and acquired full volume images with a matrix array transducer (X7-2, X5-1, or X3-1). The experienced doctors or sonographers in the pediatric or adult cardiology field recorded all images. Full volume datasets were acquired from the apical window with the subject in the left lateral decubitus position. For measuring the LAV, the frame rate on the RT3DE was 22.2 ± 5.2 frames/sec. The 3D datasets were transferred to a commercially available quantitative software (3DQ Adv, QLAB, version 9; Philips Medical System). Subsequently, 5-point markings, including the septal, lateral, anterior, and inferior corners of the mitral annulus and the roof of the LA wall, were performed; the endocardial border was automatically delineated, and the LAV was measured throughout the one cardiac cycle. Manual adjustment of the endocardial border was performed when necessary to exclude the pulmonary vein in the LA cavity. We measured the maximum and minimum LAV during the cardiac cycle. The LA distensibility was calculated by the equation (maximum LAV – minimum LAV)/minimum LAV × 100. Each parameter was indexed according to body surface area (BSA), when appropriate.

Intra-observer and inter-observer variability

For the intra-observer variability, the same observer analyzed the datasets again 1 week after the first measurement in the same cardiac cycle, which was blinded to the observer. The inter-observer variability was also determined by the analysis between 2 independent blinded observers (T. N. and K. A.).

Statistical analysis

Statistical analysis was performed using commercially available statistical software SPSS version 17.0 (SPSS, Inc., Chicago, IL, USA). The continuous data are expressed as mean ± standard deviation and categorical data, as absolute numbers and percentages. Univariate regression analysis was used to assess exponential and linear correlations between age, BSA, and the echocardiographic parameters. Reliability was assessed using Bland-Altman analysis and intraclass correlation coefficient (ICC), with a 95%

confidence interval. Data between 2 groups were compared using t tests. P values < 0.05 were considered statistically significant.

Results

RT3DE feasibility for LAV analysis

From a total of 345 subjects, 25 subjects were excluded due to inadequate delineation of the chamber wall in the LA images. The RT3DE feasibility for LAV measurement was 93%.

Values of RT3DE parameters and their relationship with age and BSA

The clinical characteristics and 2D echocardiographic measurements in 345 healthy subjects by overall age groups are listed in Tables 1 and 2. The 3D echocardiographic measurements of LAV in the study population are shown in Table 3. LA volumes were indexed to BSA (LAVI). Both the maximum LAVI and minimum LAVI were significantly different among the age groups. Both the maximum and minimum LAV index linearly increased with age. (maximum LAV index: $r = 0.15$; $p < 0.006$, minimum LAV index: $r = 0.41$; $p < 0.0001$) (Figure 1) While, the LAV correlation curves according to age and BSA are shown in Figure 2. Both the maximum and minimum LAVs exponentially increased with age (maximum LAV: $r = 0.66$, minimum LAV: $r = 0.68$; $p < 0.0001$) and linearly increased with increasing BSA (maximum LAV: $r = 0.69$, minimum LAV: $r = 0.66$; $p < 0.0001$) (Figure 2A, B). LA distensibility (173.1 ± 58.7%) decreased with age (LA distensibility: $r = -0.39$; $p < 0.0001$) and BSA (LA distensibility: $r = -0.35$; $p < 0.0001$) (Figure 2C).

Comparison of the RT3DE and 2D biplane Simpson's method

Figure 3 shows the agreement of LAV measurements obtained using RT3DE and 2DE. The 95% confidence intervals for the maximum and minimum LAV were -25.0 to 12.0 mL and -13.4 to 7.8 mL, respectively. The LAVs measured by RT3DE were significantly smaller than those measured by the 2D biplane Simpson's method (maximum LAV: $r = 0.78$, bias ± limits of agreements [LOA] = -6.5 ± 18.5 mL; minimum LAV: $r = 0.75$, bias ± LOA = -2.8 ± 10.6 mL). The Bland-Altman plots revealed that the tendency of the overestimation was founded greatly according to the LAV increase.

Intraobserver and interobserver variability

The intraobserver and interobserver variability were assessed in 42 randomly selected subjects (mean age, 6.3 ± 3.7 years, range, 0.1–14 years, 19 male subjects) and the results are shown in Table 4. Figures 4 and 5 show the linear correlations and results of the Bland-Altman analyses. The 3D volumetric method was proven to have favorable intraobserver (maximum LAV: $r = 0.95$, bias ± LOA = 0.10 ± 4.2 mL; minimum LAV: r

= 0.89, bias ± LOA = -0.14 ± 2.3 mL) and interobserver agreement (maximum LAV: r = 0.94, bias ± LOA = -0.18 ± 3.9 mL; minimum LAV: r = 0.93, bias ± LOA = 0.24 ± 1.9 mL).

Discussion

This study determined the normal range of the LAV and LA function using RT3DE in a large population of healthy subjects and the developmental changes in the LAV from early infancy to late adulthood. The major findings in this study are as follows: (1) the LAV increased with age and increasing BSA; (2) the LA distensibility mildly decreased with age and increasing BSA; (3) The LAVs measured by RT3DE were significantly smaller than those measured by the 2D biplane Simpson's method; and (4) the RT3DE method is reproducible and feasible for evaluating the LAV in children.

Advantages of RT3DE

RT3DE is a superior tool for the precise evaluation of complex-shaped chambers undergoing dynamic changes, such as the LA and left ventricle (LV) in children. Until recently, LAV calculations using 2DE have been recommended as the standard methods (area-length and the biplane Simpson's method); however, the shape and area of the LA obtained from 2DE images are affected by the location and direction of the transducer toward the LA maximum axis. Recently, RT3DE, which is closely associated with MRI, has provided accurate quantification of the LV and LA volume, mass, and output in adults[10-19]. The utility of cardiac MRI and computed tomography (CT) in children could be restricted, particularly due to the time required, need of sedation, and radiation exposure (CT only). RT3DE offers an opportunity for rapid, noninvasive, physiologic image acquisition with high image quality and good reproducibility.

In our study, the LAVs measured by RT3DE were significantly smaller than those measured by the 2D biplane Simpson's method, and the difference was founded greatly on the LAV increase. Therefore, the larger 2D plane of the LA is supposed to be cropped by using 2DE. Recommendations of the American Society of Echocardiography Committee indicate that volume assessment using the 2D biplane Simpson's method has the limitations of image plane positioning errors and geometric assumptions[20]. The 2D biplane Simpson's method is acceptable at least for normal-shaped hearts as reported by Fukuda et al[8]. However, Iwataki et al reported that the 2D biplane Simpson's method overestimates the LAV due to misalignment of the 2D cutting plane, and the 3D volumetric method is a more reliable way to accurately evaluate LAV[21]. In any case, it is not possible to correctly measure the LAV because LA shape is very complicated and varied. To our knowledge, our study is the first to identify normal LAV values using RT3DE in large healthy children. Based on our results, RT3DE could be a more feasible tool and reproducible method than those that are currently used in the clinical and research field of congenital heart disease.

Relationship with age and BSA

It is generally accepted that age-related changes in cardiac structure and function occur in healthy subjects[8, 19]. We found that both the maximum and minimum LAVs increased with age and increasing BSA. Our results of age- and BSA-related changes of the heart are consistent with the findings of previous studies in normal subjects using 2DE[3, 8]. We reported that LA distensibility have a weak negative linear correlation with aging and increasing BSA. A high LA distensibility could fill up a smaller LAVI, highlighting LA function in children. Hisao et al reported that the LA distensibility are superior and valuable diastolic parameters for identifying high LVFP compared with E/e'[22, 23]. Our study also provides the age- and BSA-related reservoir function of the LA in healthy children, which are basic and important parameters when considering atrial and diastolic function in patients with congenital heart disease.

Further studies

This study provides the normal range of the maximum and minimum LAV using RT3DE in children and adults and the changes in the maximum and minimum LAV from early infancy to adulthood. Further studies are necessary to assess the dynamic changes in the LAV during the cardiac cycle and to analyze the LA reservoir, conduit, and booster pump function in healthy children. Furthermore, the LA function in children with congenital heart disease should be analyzed.

Study limitations

Several limitations should be mentioned. First, we could not validate the LAV measurements by comparing the RT3DE and MRI measurements in children. The accurate LA volume measurements using MRI were required for the understanding of the difference of LA volume between 2DE and RT3DE measurements, however, the healthy volunteer of small children could not be sedated so long time for MRI ethically. Furthermore, to evaluate the maximum and minimum LAV more accurately, further technological advancements to increase the volume rate, both in 3DE and MRI, are required. Second, we acquired full volume images using only iE-33 in all subjects. There are no data on the differences between ultrasound vendors concerning LAV analysis in children and therefore, this might influence the reproducibility of our results.

Conclusions

The reference values of the LAV from early infancy to adulthood were obtained using RT3DE and could be useful for future clinical practice and research in children with congenital heart disease. RT3DE is a reproducible method and a feasible tool for the evaluation of the LAV in children. Moreover, the LA distensibility could possibly decrease with age and increasing BSA.

REFERENCES

1. Moller JE, Hillis GS, Oh JK, et al: Left atrial volume: a powerful predictor of survival after acute myocardial infarction. Circulation 2003:107:2207–12.
2. Tsang TS, Abhayaratna WP, Barnes ME, et al: Prediction of cardiovascular outcomes with left atrial size: is volume superior to area or diameter? J Am Coll Cardiol 2006:47:1018-23.
3. Abhayaratna WP, Seward JB, Appleton CP, et al: Left Atrial Size. J Am Coll Cardiol 2006:47:2357-63.
4. Murata M, Iwanaga S, Tamura Y, et al: A real-time three-dimensional echocardiographic quantitative analysis of left atrial function in left ventricular diastolic dysfunction. Am J Cardiol 2008:102:1097-1102.
5. Mochizuki A, Yuda S, Oi Y, et al: Assessment of left atrial deformation and synchrony by three-dimensional speckle-tracking echocardiography: comparative studies in healthy subjects and patients with atrial fibrillation. J Am Soc Echocardiogr 2013:26:165-74.
6. Mor-Avi V, Sugeng L, Lang RM: Real-time 3-dimensional echocardiography: an integral component of the routine echocardiographic examination in adult patients? Circulation 2009:119:314-29.

7. Russo C, Hahn RT, Jin Z, et al: Comparison of echocardiographic single-plane versus biplane method in the assessment of left atrial volume and validation by real time three-dimensional echocardiography. J Am Soc Echocardiogr 2010:23:954-60.
8. Fukuda S, Watanabe H, Daimon M, et al: Normal values of real-time 3-dimensional echocardiographic parameters in a healthy Japanese population: the JAMP-3D Study Circ J. 2012:76:1177-81.
9. Cameli M, Lisi M, Righini FM, et al: Novel echocardiographic techniques to assess left atrial size, anatomy and function. Cardiovasc Ultrasound 2012:10:4.
10. Sugeng L, Mor-Avi V, Weinert L, et al: Quantitative assessment of left ventricular size and function: side-by-side comparison of real-time three-dimensional echocardiography and computed tomography with magnetic resonance reference. Circulation 2006:114:654-61.
11. Lin FY, Devereux RB, Roman MJ, et al: Cardiac chamber volumes, function, and mass as determined by 64-multidetector row computed tomography: mean values among healthy adults free of hypertension and obesity. JACC Cardiovasc Imaging 2008:1:782-6.
12. Artang R, Migrino RQ, Harmann L, et al: Left atrial volume measurement with

automated border detection by 3-dimensional echocardiography: comparison with Magnetic Resonance Imaging. Cardiovasc Ultrasound 2009:7:16.

13. Miyasaka Y, Tsujimoto S, Maeba H, et al: Left atrial volume by real-time three-dimensional echocardiography: validation by 64-slice multidetector computed tomography. J Am Soc Echocardiogr 2011:24:680-6.
14. Mor-Avi V, Yodwut C, Jenkins C, et al: Real-time 3D echocardiographic quantification of left atrial volume: multicenter study for validation with CMR. JACC Cardiovasc Imaging 2012:5:769-77.
15. Corsi C, Lang RM, Veronesi F, et al: Volumetric quantification of global and regional left ventricular function from real-time three-dimensional echocardiographic images. Circulation 2005:112:1161-70.
16. Sugeng L, Mor-Avi V, Wienert L, et al: Quantitative assessment of left ventricular size and function: side-by-side comparison of real-time three-dimensional echocardiography and computed tomography with magnetic resonance reference. Circulation 2006:114:654-61.
17. Takeuchi M, Nishikage T, Mor-Avi V, et al: Measurement of left ventricular mass by real-time three-dimensional echocardiography: validation against magnetic resonance and comparison with two-dimensional and m-mode

measurements. J Am Soc Echocardiogr 2008:21:1001-5.

18. Kaku K, Takeuchi M, Otani K, et al: Age- and gender-dependency of left ventricular geometry assessed with real-time three-dimensional transthoracic echocardiography. J Am Soc Echocardiogr 2011:24:541-7.

19. Lang RM, Bierig M, Devereux RB, et al: Recommendations for Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjuction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005:18:1440-1463.

20. Iwataki M, Takeuchi M, Otani K, et al: Measurement of left atrial volume from transthoracic three-dimensional echocardiographic datasets using the biplane Simpson's technique. J Am Soc Echocardiogr 2012:25:1319-26.

21. Hsiao SH, Huang WC, Lin KL, et al: Left atrial distensibility and left ventricular filling pressure in acute versus chronic severe mitral regurgitation. Am J Cardiol 2010:105:709-15.

22. Hsiao SH, Chiou KR, Lin KL, et al: Left atrial distensibility and E/e' for estimating left ventricular filling pressure in patients with stable angina. -A comparative echocardiography and catheterization study-. Circ J

2011:75:1942-50.

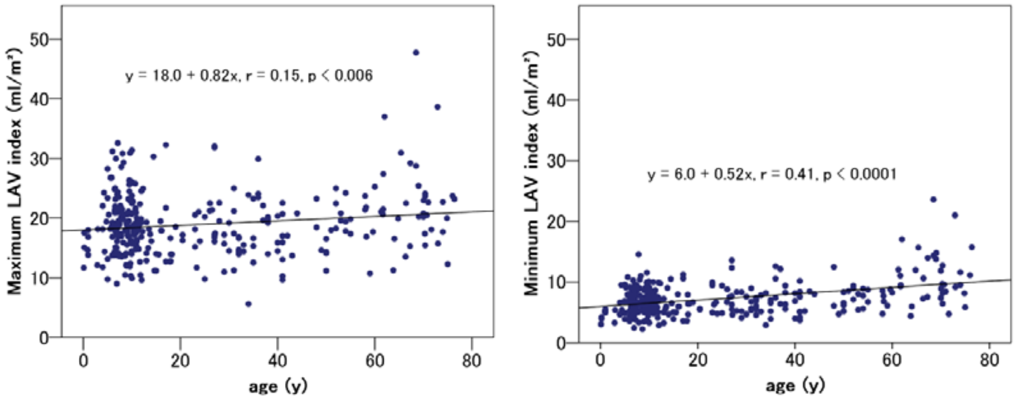

Figure 1. Correlation of maximum and minimum LAV index using RT3DE with age

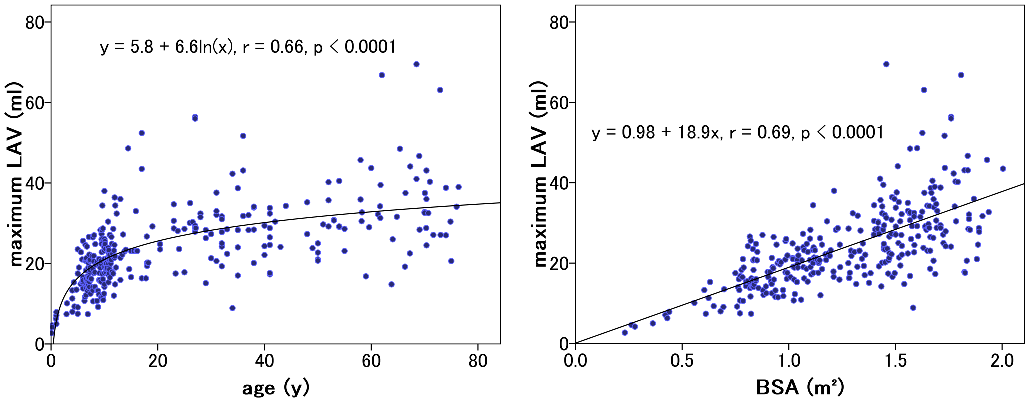

Figure 2A. Correlation of maximum LAV using RT3DE with age and increasing BSA

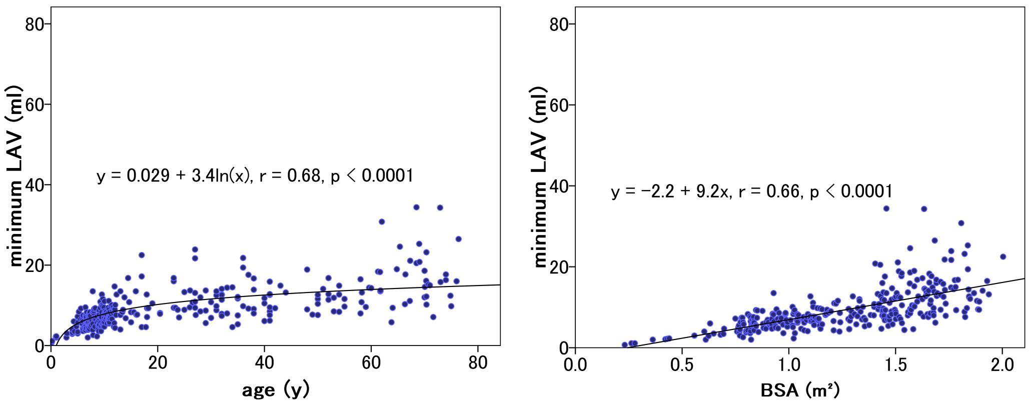

Figure 2B. Correlation of minimum LAV using RT3DE with age and increasing BSA

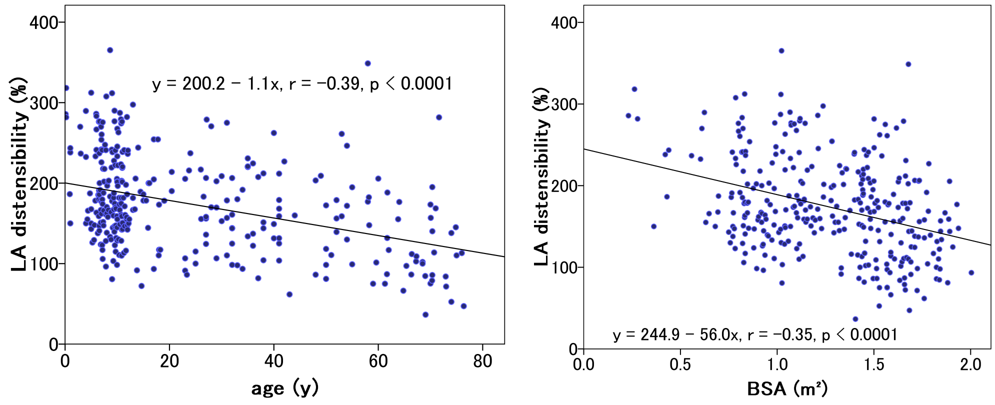

Figure 2C. Correlation of LA distensibility using RT3DE with age and increasing BSA

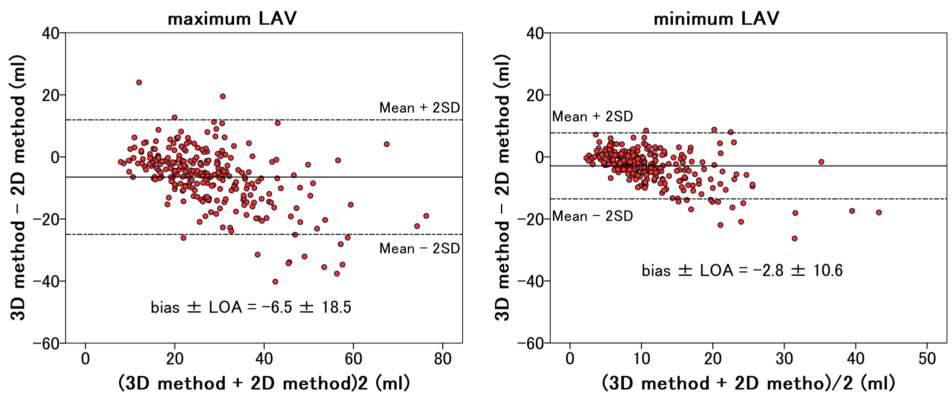

Figure 3. The agreement of LAV measurements between RT3DE and 2DE

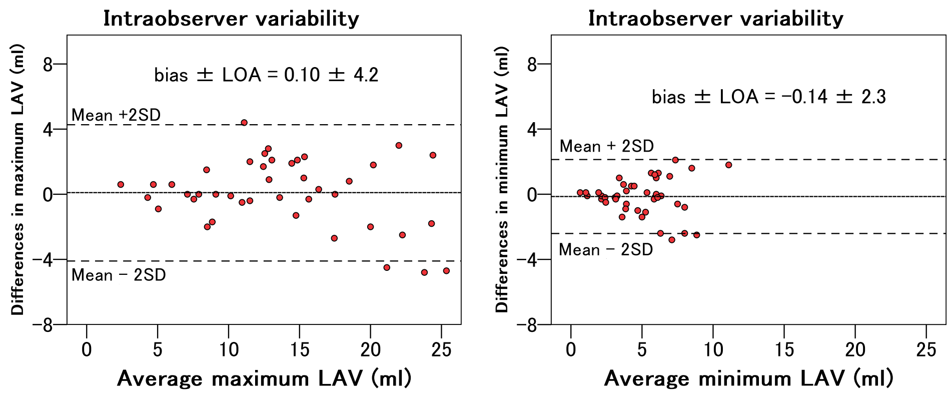

Figure 4. Intra-observer variability

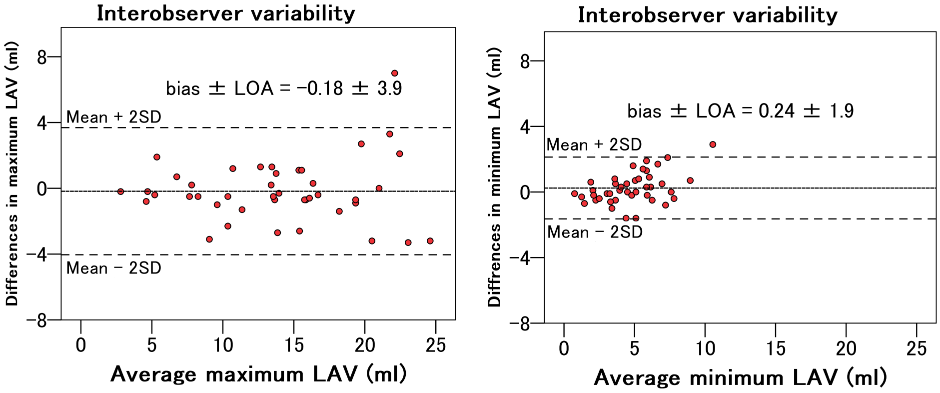

Figure 5. Inter-observer variability

Table 1 Clinical characteristics

Age group (years)	over all	0 - 5	5 – 10	10 – 20	20 – 40	40 – 60	60 - 80	P value
	Total subjects (n = 345)							
n		16	107	82	59	42	39	
men	166 (48%)	9 (56.3%)	51(47.7%)	39 (47.6%)	26 (44.1%)	20 (47.6%)	21 (53.8%)	< 0.0001
BSA (m^2)	1.3 ± 0.37	0.50 ± 0.16	0.94 ± 0.14	1.29 ± 0.22	1.61 ± 0.18	1.61 ± 0.15	1.58 ± 0.13	< 0.0001
Height (cm)	143.5 ± 23.0	84.0 ± 18.0	124.8 ± 9.1	148.6 ± 11.9	164.4 ± 9.7	162.6 ± 8.0	158.3 ± 7.9	< 0.0001
Weight (kg)	41.2 ± 17.3	11.0 ± 4.4	25.5 ± 6.4	40.8 ± 11.2	56.9 ± 9.7	58.2 ± 8.7	57.2 ± 7.3	< 0.0001
Heart Rate (beats/min)	78.6 ± 15.2	102.8 ± 22.3	79.2 ± 11.5	73.2 ± 13.7	82.6 ± 14.8	77.3 ± 13.3	73.8 ± 14.9	< 0.0001
Systolic BP (mmHg)	115.3 ± 16.7	104.4 ± 9.9	103.0 ± 9.1	110.8 ± 12.2	123.3 ± 13.3	127.0 ± 15.2	133.6 ± 16.7	< 0.0001
Diastolic BP (mmHg)	64.8 ± 11.2	64.0 ± 8.6	59.4 ± 9.2	59.3 ± 7.4	67.9 ± 10.7	75.2 ± 8.7	74.7 ± 9.7	< 0.0001

BSA, body surface area; BP, blood pressure

Data are expressed as mean ± SD or as number (percentage)

Table 2 2D echocardiographic measurements

Age group (years)	over all	0 - 5	5 – 10	10 – 20	20 – 40	40 – 60	60 - 80	P value
	Total subjects (n = 345)							
n		16	107	82	59	42	39	
LVDd (cm)	41.0 ± 6.6	28.7 ± 5.8	37.7 ± 4.4	42.9 ± 4.1	43.6 ± 5.5	43.9 ± 5.9	46.7 ± 5.1	< 0.0001
LVDs (cm)	25.6 ± 5.8	17.5 ± 3.9	23.8 ± 3.8	26.7 ± 3.4	27.6 ± 6.6	28.4 ± 7.0	26.9 ± 7.3	< 0.0001
E (cm/s)	93.8 ± 24.0	98.9 ± 19.6	105.4 ± 20.2	104.4 ± 16.8	91.7 ± 18.7	74.6 ± 22.4	65.7 ± 18.3	< 0.0001
A (cm/s)	52.2 ± 16.5	60.4 ± 16.2	47.7 ± 11.7	42.9 ± 9.5	48.7 ± 11.6	58.7 ± 16.1	76.5 ± 18.0	< 0.0001
e’ sept (cm/s)	11.7 ± 29.3	9.4 ± 1.9	13.2 ± 1.7	13.9 ± 1.6	12.0 ± 1.7	9.2 ± 1.7	6.7 ± 1.5	< 0.0001
a’ sept (cm/s)	6.9 ± 2.4	6.4 ± 1.7	5.3 ± 1.4	5.1 ± 1.3	8.3 ± 1.8	9.4 ± 2.2	9.6 ± 1.6	< 0.0001
E/A	2.0 ± 0.80	1.7 ± 0.48	2.3 ± 0.63	2.6 ± 0.72	2.0 ± 0.60	1.3 ± 0.45	0.90 ± 0.30	< 0.0001
E/e’	8.3 ± 2.2	10.6 ± 1.7	8.1 ± 1.9	7.5 ± 1.3	7.8 ± 1.9	8.3 ± 2.5	10.2 ± 2.8	< 0.0001
LVEDV (ml)	86.7 ± 29.9	37.4 ± 9.7	65.5 ± 15.4	95.3 ± 30.8	96.9 ± 25.0	93.2 ± 23.4	110.8 ± 33.3	< 0.0001
LVESV (ml)	33.1 ± 12.5	15.9 ± 4.2	25.9 ± 6.4	36.0 ± 11.7	37.2 ± 11.0	36.1 ± 12.6	39.3 ± 17.4	< 0.0001
LVEDVI (ml/m^2)	66.6 ± 14.4	62.9 ± 5.1	69.4 ± 10.6	74.1 ± 13.1	60.4 ± 14.5	58.0 ± 14.3	67.9 ± 17.4	< 0.0001
LVESVI (ml/m^2)	25.6 ± 6.9	27.1 ± 2.4	27.5 ± 4.9	28.6 ± 6.7	23.2 ± 6.6	22.4 ± 7.5	22.8 ± 8.4	< 0.0001
LVEF (%)	61.8 ± 6.5	57.3 ± 2.3	60.5 ± 3.8	62.0 ± 3.8	62.7 ± 5.8	62.1 ± 8.2	64.1 ± 12.3	0.061

Maximum LAV (ml)	31.3 ± 15.0	12.9 ± 6.0	20.8 ± 6.8	30.6 ± 12.2	38.0 ± 13.3	39.3 ± 13.3	46.0 ± 17.4	< 0.0001
Minimum LAV (ml)	12.6 ± 8.2	4.0 ± 2.4	7.6 ± 3.2	12.3 ± 7.6	14.5 ± 6.3	15.7 ± 5.9	22.2 ± 11.8	< 0.0001
Maximum LAVI (ml/m^2)	23.7 ± 7.4	21.6 ± 8.9	22.0 ± 5.8	24.1 ± 7.1	24.2 ± 7.9	24.2 ± 7.9	28.0 ± 9.3	0.006
Minimum LAVI (ml/m^2)	9.3 ± 4.4	6.7 ± 3.6	8.0 ± 2.8	9.5 ± 4.4	9.0 ± 3.6	9.7 ± 3.6	13.5 ± 6.8	< 0.0001
LAEF (%)	61.3 ± 10.7	69.8 ± 5.0	63.8 ±7.9	61.3 ± 11.4	62.5 ± 9.6	60.0 ± 8.5	52.8 ± 14.6	< 0.0001

LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; E, early diastolic mitral flow velocity; A, late diastolic mitral flow velocity; e' sept, ealy diastolic septal annular velocity; a' sept, late diastolic septal annular velocity; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; LAV, left atrial volume; LAVI, left atrial volume index Data are expressed as mean ± SD or as number (percentage)

Table 3 3D echocardiographic measurements of LA parameters

Age group	Total subjects (n = 320)							
(years)	Over all	0 – 5	5 - 10	10 – 20	20 – 40	40 – 60	60 – 80	P value
n		15	60	78	53	37	36	
Maximum LAV (ml)	24.0 ± 10.1	8.4 ± 3.7	18.0 ± 5.3	23.2 ± 7.3	29.4 ± 9.0	28.6 ± 6.5	35.9 ± 12.2	< 0.0001
Minimum LAV (ml)	9.4 ± 5.1	2.7 ± 1.4	6.5 ± 2.2	8.4 ± 3.1	11.4 ± 4.2	11.4 ± 3.1	17.3 ± 6.9	< 0.0001
Maximum LAVI (ml/m^2)	18.9 ± 5.3	16.5 ± 3.7	19.3 ± 5.2	18.1 ± 4.5	18.2 ± 5.1	17.8 ± 4.0	22.6 ± 7.4	< 0.0001
Minimum LAVI (ml/m^2)	7.2 ± 2.7	5.2 ± 1.6	6.9 ± 2.1	6.5 ± 1.7	7.0 ± 2.3	7.1 ± 1.9	10.9 ± 4.2	< 0.0001
LAEF (%)	61.7 ± 8.6	68.4 ± 5.7	64.0 ± 6.7	63.6 ± 6.8	61.0 ± 7.7	59.6 ± 8.9	51.9 ± 10.4	< 0.0001
LA distensibility (%)	173.1 ± 58.7	221.9 ± 54.9	188.1 ± 56.0	183.8 ± 51.8	166.2 ± 51.9	159.9 ± 60.0	118.5 ± 51.2	< 0.0001

Abbreviations see in Table 2

Data are expressed as mean ± SD or as number (percentage)

Table 4 Intra- and inter-observer variability

			P value	Bias (95% LOA)	ICC
Intra-observer variability	1st	2nd			
Maximum LAV (ml)	13.8 ± 5.8	13.7 ± 6.4	< 0.0001	0.10 (-4.1 to 4.3)	0.947
Minimum LAV (ml)	4.9 ± 2.4	5.0 ± 2.4	< 0.0001	-0.15 (-2.4 to 2.2)	0.941
Inter-observer variability	Observer 1 (T. N)	Observer 2 (K. A)			
Maximum LAV (ml)	13.8 ± 5.8	13.9 ± 5.7	< 0.0001	-0.18 (-4.1 to 3.9)	0.944
Minimum LAV (ml)	4.9 ± 2.4	4.6 ± 2.0	< 0.0001	0.24 (-1.7 to 2.1)	0.926

ICC, intraclass Correlation Coefficient; LOA, limits of agreement

Abbreviations see in Table 2