Assessment of fetal left atrial volume and function using a novel left atrial volume tracking method

Xiaohui Peng[1], Suping Zhou[2], Jiaoni Wang[1], Mei Pan[1], Bei Wang[1], Xiaolu Sun[1], Bowen Zhao[1]

[1]Department of Diagnostic Ultrasound and Echocardiography, Sir Run Run Shaw Hospital, Zhejiang University Medical College, Hangzhou, China
[2]Department of Diagnostic Ultrasound, Peking University Shenzhen Hospital, Shenzhen, China

Correspondence to:
Bowen Zhao, MD,
Department of Diagnostic Ultrasound and Echocardiography, Sir Run Run Shaw Hospital, Zhejiang University Medical College,
3 Qingchun Road East, Hangzhou, Zhejiang Province, China,
phone: +86 571 86 006 331,
e-mail: zbwcjp@zju.edu.cn

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ABSTRACT

Background: Several fetal cardiovascular structural defects may alter the hemodynamics of the cardiac chambers resulting in changes in chamber sizes. Quantitative measurements of the sizes of cardiac chambers can augment the diagnostic power of fetal echocardiography.

Aims: Using a new left atrial volume tracking (LAVT) method, time-left atrial volume curves (TLAVCs) can be automatically obtained. The goal of this study was to examine whether this method can be used to evaluate left atrial volume (LAV) and provide reference values for LAV and indices of left atrial function in normal human fetuses.

Methods: Two hundred and four normal human fetuses were enrolled. Using LAVT, the maximal left atrial volume (LAVmax) and minimal left atrial volume (LAVmin) were measured from TLAVCs. Left atrial ejection fraction (EF) was calculated. The maximal left atrial area (LAAmax) and minimal left atrial area (LAAmin) were measured using manual method tracing.

Results: Between 21 and 40 weeks, mean LAVmax increased from 0.27 ml to 4.15 ml, and mean LAVmin increased from 0.13 ml to 2.26 ml, respectively, while the EF remained stable at around 0.43. From 21 to 40 weeks, mean LAAmax increased from 0.61 cm^2 to 2.64 cm^2, and mean LAAmin increased from 0.34 cm^2 to 1.53 cm^2.

Conclusions: This study establishes reference values for fetal LAV during the second half of gestation. The LAVT method appears to be feasible in estimating fetal LAV and shows potential for assessing left atrial function.

Key words: fetal echocardiography, left atrial tracking, left atrial volume

INTRODUCTION

Fetal echocardiography has become a reliable technique for assessing structural defects and arrhythmias in the second and third trimesters of gestation [1–2]. Several fetal cardiovascular structural defects and arrhythmias may alter the hemodynamics of the atrial and/or ventricular chambers resulting in changes in chamber sizes [3–6]. The size and shape of the chambers in fetuses are related to perinatal death [7]. Quantitative measurements of the sizes of cardiac chambers may enable the physician to understand the growth pattern of normal fetal hearts and augment the diagnostic power of fetal echocardiography. Traditional methods include measurements of the diameters of cardiac chambers by M-mode and 2-dimensional echocardiography (2DE) methods [8–9]. Chamber volume calculation from 2DE does not rely on measuring a single dimension, but rather covers the entire cross-sectional area of the chamber; therefore, measurements using 2DE may better estimate volume changes. The accuracy of ventricular volume determination by 2DE using a biplane Simpson's rule algorithm was first shown in fetal sheep [10], and then this method was further developed in normal human fetuses [11]. In adults, the 2DE biplane Simpson's method was recommended by the American Society of Echocardiography to evaluate left atrial volume (LAV), and the accuracy has been validated by in-vitro models and angiography [12–14]. The left atrial volume tracking (LAVT) method is a newly developed method that is an automated measurement. It is evaluated

WHAT'S NEW?

In adults, 2-dimensional echocardiography (2DE) biplane Simpson's method was recommended by the American Society of Echocardiography to evaluate left atrial volume (LAV) and the accuracy has been validated by in-vitro models and angiography. This study applies a new left atrial volume tracking (LAVT) method, which is based on Simpson's rule algorithm, to establish normal values for human LAV during the second half of gestation. The LAVT method appears to be a feasible method to estimate fetal LAV and left atrial ejection fraction (EF) during the second half of gestation, suggesting its potential value in assessing left ventricular diastolic function of fetal hearts, especially under pathological conditions in the mother or fetus.

in images based on offline analysis and might be useful for measuring LAV curves precisely in adults [15]. Recently, it has also been used in fetal hearts [16–17]. In our study, we apply this method, which is based on Simpson's rule algorithm, to establish normal values for human LAV during the second half of gestation.

METHODS

Study population

The study population consisted of singleton pregnancies from 21 to 40 weeks of gestation undergoing fetal echocardiography scans at the Sir Run Run Shaw Hospital, Zhejiang University College of Medicine in Hangzhou, China. This study was approved by the Ethics Committee of the Sir Run Run Shaw Hospital and informed consent was obtained from all participants. Inclusion criteria were accurate gestational age (GA) based upon measurement of the fetal biparietal diameter (BPD) and femoral length; normal fetal growth, and absence of medical complications, such as diabetes mellitus, or hypertension. The exclusion criteria were fetal cardiac and extracardiac abnormalities; abnormal intrauterine fetal growth; inability to obtain a standard view due to variable fetal position.

A total of 204 fetuses that had normal cardiac morphology and normal sinus rhythm in the second and third trimesters were used as the research objects. Inspection of the atrial symmetry would be first made in a standard four-chamber heart view. If there was any asymmetry in atrial size, we would measure the width and length of the left and right atrium and then calculate the width ratio of the left and right atrium (RA/LA width ratio); if the RA/LA width ratio was in the range of 0.8~1.2, the fetus was regarded as having normal atrial morphology.

The principles of the left atrial volume tracking method

The LAVT method uses the adaptive density gradient (ADG) method with the ability of automatic construction of the LAV profile by applying a 2-dimensional tissue tracking technique. In the ADG method [18], only the pixels on the sector beam which has the necessary information for the tracking process would be tracked, resulting in reducing the number of pixels for tracking and saving tracking time (Supplementary material, *Video S1*). Therefore, the ADG method can produce faster calculation speed, higher accuracy, and higher frame rates compared to the conventional block-matching method [18]. An image clip of the apical four-chamber view in one cardiac cycle was stored in the commercially available EUB-900 ultrasound scanner (Hitachi Medical Corporation, Chiba, Japan). The automatic construction of the left atrial curve was performed offline using a prototype viewer (Hitachi Medical Corporation, Chiba, Japan). The left atrial endocardium was manually traced at first, and subsequent LAV at each frame was automatically calculated by the single-plane Simpson's rule, resulting in the construction of the LAV curve within one minute. The biplane Simpson's rule can also be applied in this procedure.

Echocardiography

Echocardiographic examinations were performed on the subjects with a Philips iE33 xMATRIX ultrasound system (Philips Medical System, Bothell, WA, USA) with a 1.0–5.0 or 3.0–8.0 MHz transducer. General schematic sonographic examination was performed to rule out fetal abnormalities and was followed by detailed fetal 2-dimensional and color Doppler echocardiography to exclude fetal heart anomalies [19]. The maximal left atrial area (LAAmax) and minimal left atrial area (LAAmin) were traced from the four-chamber view. We magnified the images to minimize calibration-induced measurement errors. Then, we used the commercially available EUB-900 ultrasound scanner (Hitachi Medical Corporation, Chiba, Japan) to obtain time-left atrial volume curves (TLAVCs). The fetal left atrium was imaged in orthogonal planes corresponding to those obtained postnatally for volume calculation equivalent to apical four- and two-chamber views. Imaging of the left atrium was considered satisfactory if all 4 chambers, the left ventricular apex, both atrioventricular valves, and confluence of pulmonary veins were seen in the four-chamber view. The display of the mitral valve, apex, and aortic valve served as coordinates in the two-chamber view. After optimizing the gain, dynamic range, and sensitivity time control, images were digitally recorded for 2 seconds (about 5 to 6 cardiac cycles) and stored on hard discs for later analysis. Then, the left atrial endocardium of the apical four-chamber and two-chamber view was manually traced at the first frame. This measurement was based on the innermost bright edge convention, which disregarded the orifices of the pulmonary veins but not the floating foramen ovale flap. Subsequently, LAV at each frame was

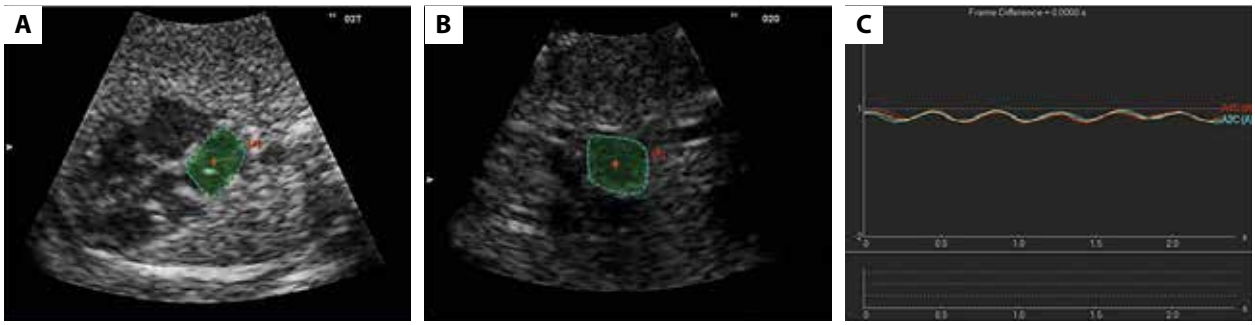

Figure 1. The manual trace of the left atrial endocardium at the level of four-chamber (**A**) and 2-chamber view (**B**) at the first frame of the dynamic images. Time-left atrial volume curves (**C**) were automatically obtained with the left atrial tracking method, which contained the volume corresponding to each frame, including the volume in 4-chamber view (the red curve), 2-chamber view (the blue curve) and the overall volume (the yellow curve) by the biplane Simpson's rule.

automatically calculated by the single-plane and biplane Simpson's rule. Finally, TLAVCs were automatically obtained (Figure 1). The LAVmax and LAVmin were measured from the volume waveform by the biplane Simpson's rule. Calculations were made in 3 to 6 consecutive cardiac cycles and averaged. Left atrial EF was calculated as the difference between LAVmax and LAVmin, divided by end-diastolic volume. In 20 randomly selected fetuses, both LAVmax and LAVmin were measured by the same observer (B.W.Z) twice and then by another observer (SPZ) to compare the measurements and to calculate interobserver and intraobserver agreement.

Statistical analysis

For each variable, a simple scatter plot graph was first obtained to observe roughly their correlations and tendencies with GA. Regression analysis was used to examine the correlation between measured volumes and GA and measured volumes and BPD. Separate linear, quadratic, cubic, and logarithmic regression models were fitted to identify the optimal one. Based on the equations acquired for both the mean and SD, population reference intervals for gestational age were estimated. Bland-Altman analysis was used to compare the measurement agreement and bias for a single observer and two observers [20–21]. P <0.05 was considered statistically significant. The data were analyzed using Excel for Windows 2003 (Microsoft Corp., Redmond, WA, USA) and IBM SPSS package 22.0 (SPSS, Inc., Chicago, IL, US).

RESULTS

Of all 204 fetuses, 17 fetuses were excluded because of inadequate imaging. Optimal TLAVCs were acquired in the other 187 fetuses (success rate was 92%). Limiting factors for TLAVCs acquisition included low image resolution at young GA, abundant fetal movement, numerous acoustic shadows, and a persistent unfavorable fetal position. It was found that all the target volumes correlated strongly both with GA and BPD. The best-fitted regression equations of the mean of the studied parameters against GA and BPD are shown in Supplementary material, *Table S1*. The curves of best fit for mean LAVmax and LAVmin against both GA (Figure 2) and BPD (Figure 3) as the independent variable were the quadratic curve. Meanwhile, the best model for mean LAAmax and LAAmin based on GA was linear regression. Based on the acquired equations the predicted mean LAVmax ranged from 0.27 ml at 21 weeks to 4.15 ml at 40 weeks, and the mean LAVmin ranged from 0.13 ml at 21 weeks to 2.26 ml at 40 weeks. Figure 4 demonstrated an increase in LAAmax and LAAmin with advancing GA. The detailed values are shown in Supplementary material, *Table S2*. Meanwhile, Pearson correlation analysis showed there was no significant correlation between mean left atrial EF and GA, and it remained fairly stable at around 0.43 with advancing GA (Figure 2). Bland-Altman analysis showed that there was a good agreement of the LAV data between two observers and for a single observer. The intra-observer variation coefficient for measured mean LAVmax and LAVmin was 5.0% and 6.6%, respectively; and the interobserver variation coefficient for measured mean LAVmax and LAVmin was 7.6% and 7.9%, respectively (Figure 5).

DISCUSSION

In the present study, we examined whether the newly developed LAVT method can be used to evaluate LAV and provide normal LAV reference indices for evaluation of left atrial function in normal human fetuses. Left atrial function can best be characterized by pressure-volume loops, similar to methods used to estimate left ventricular function [22–23]. However, invasive methods for determination of instantaneous left atrial pressures are required for this evaluation. In adults, computed tomography (CT) and magnetic resonance imaging (MRI) are considered more accurate than echocardiographic methods in the quantification of LAV [12, 24]. But for fetuses, those cardiac scanning modalities are infeasible because of their inability to conduct ECG gating technology or harmful radiation effects. Thus, with the introduction of various new technologies, echocardiography has been ever widely used in screening for fetal heart diseases [2]. Several initial studies indicated the applicability of the LAVT method in assessing LAV and its usefulness has been validated in adult investi-

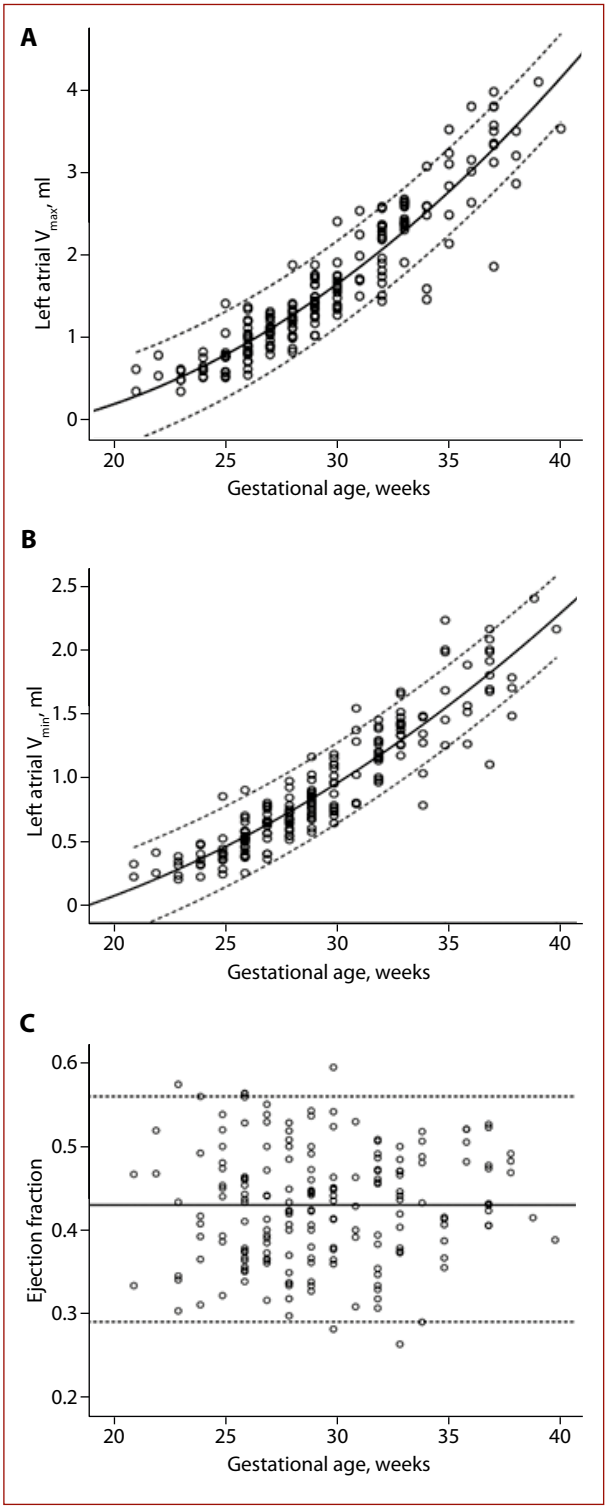

Figure 2. Volume measurements of the left atrium and ejection fraction plotted against gestational age. Atrial volume showed a consistently stronger correlation than that found with biparietal diameter (BPD). Solid lines represent the mean; dashed lines represent 5% and 95% confidence intervals (CI). **A.** Left atrial maximal volume. **B.** Left atrial minimal volume. **C.** Left atrial ejection fraction

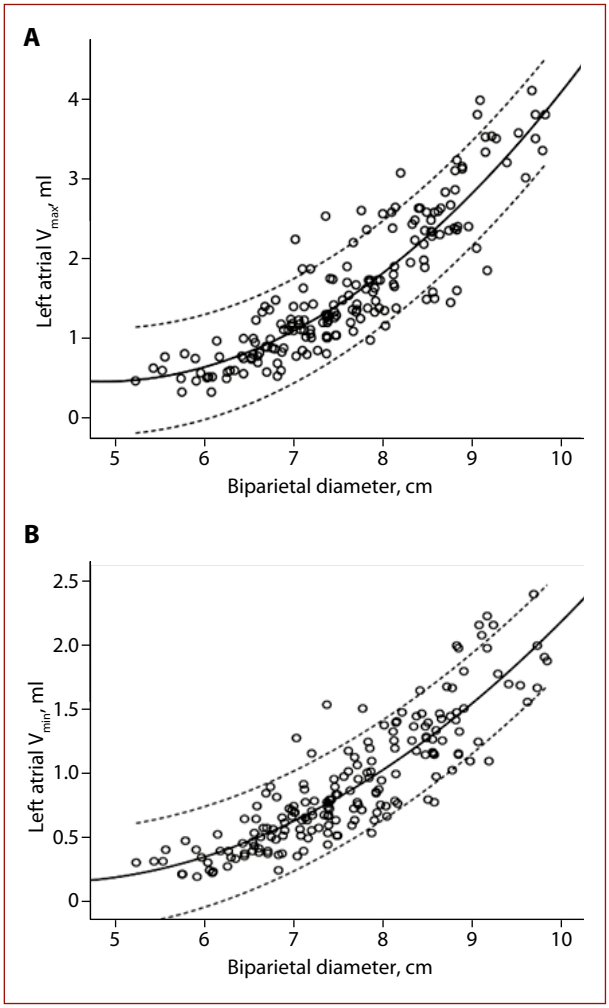

Figure 3. Volume measurements of the left atrium plotted against biparietal diameter (BPD). Solid lines represent the mean; dashed lines represent 5% and 95% confidence intervals. **A.** Left atrial maximal volume. **B.** Left atrial minimal volume

gation [15, 25–26]. To the best of our knowledge, this is the first investigation attempting to quantify LAV in a relatively large group of normal fetuses.

There was up to a 20-fold increase in fetal maximal and minimal LAV between 21 weeks and 40 weeks, which was faster during the last quarter of pregnancy. The quadratic shape of these growth curves resembles general fetal growth curves that are related to GA. However, they are different from the linear growth curves that have been reported previously for M-mode diameter measurements of the left atrial size calculated from 1 dimension [27]. The manually traced left atrial areas were found to correlate with GA. LAV increased with GA, which is consistent with our study [28–29]. It may add useful information to future

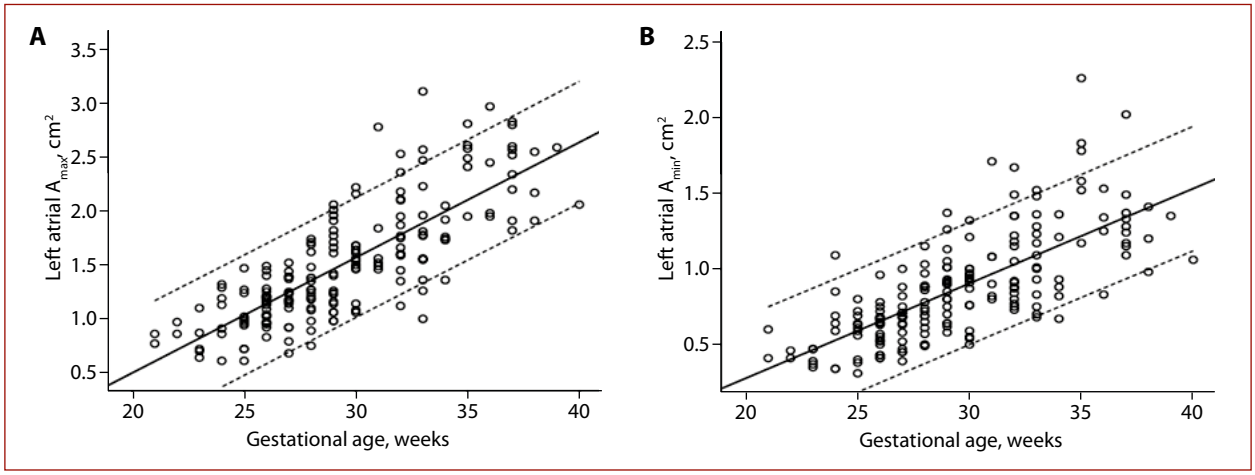

Figure 4. Area measurements of left atrium plotted against gestational age. Solid lines represent the mean; dashed lines represent 5% and 95% confidence intervals. **A.** Left atrial maximal area. **B.** Left atrial minimal area

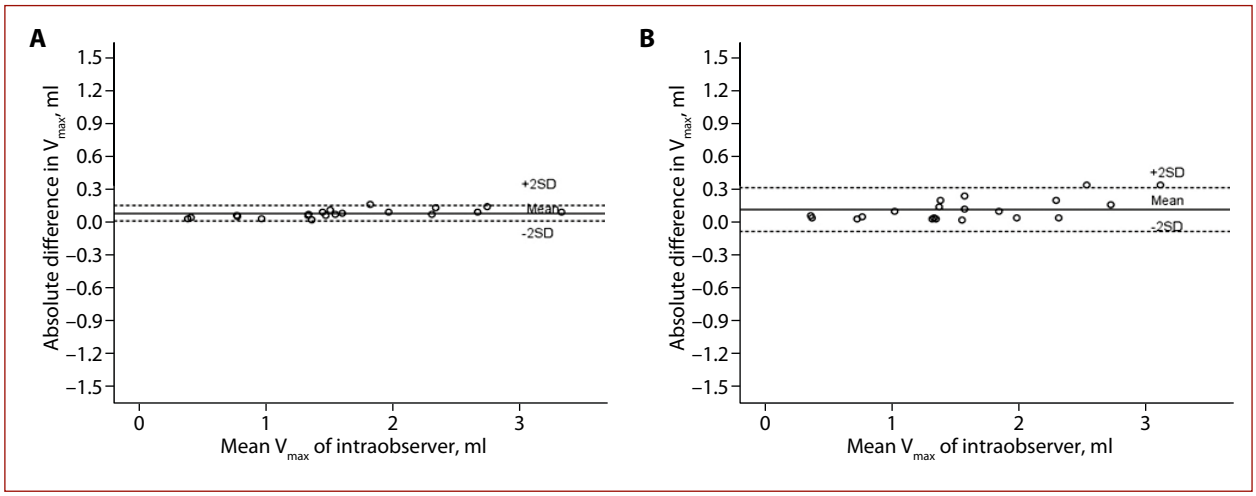

Figure 5. Bland-Altman plots of the absolute difference and 95% limits of agreement between paired measurements of left atrial Vmax by the same sonographer (**A**) and two sonographers (**B**)

studies of fetal LA [28–30]. Theoretically, left atrial mechanical function consists of three phases within the cardiac cycle [31]. First, during ventricular systole and isovolumic relaxation, the left atrium functions as a "reservoir" that receives blood from pulmonary venous return and stores energy in the form of pressure. Second, during the early phase of ventricular diastole, the left atrium operates as a "conduit" for transferring blood into the left ventricle (LV) after mitral valve opening via a pressure gradient. Third, during the late phase of ventricular diastole, LA performs as a "booster pump" through the contractile function which normally serves to augment the LV stroke volume by approximately 20% [31]. In normal adults, the TLAVCs consist of 2 peaks and 2 valleys, and phased LAV can be easily distinguished [26]. However, in fetuses that would be difficult without the guidance of the electrocardiogram since E and A waves of the diastolic mitral flow spectrum may fuse as a result of fast fetal heartbeat; thus the second valley becomes blurred in the curve (Figure 1).

In this study, as a fetal electrocardiogram cannot routinely be available, phasic left atrial functions cannot be acquired from the TLAVCs. Some studies were done with speckle tracking analysis of the atria [32, 23]. In conclusion, left atrial EF was acquired through LAVmax and LAVmin obtained from the curve, and the result showed that it remained stable with advancing GA. It resembles the growing pattern of left atrial shortening fraction calculated using the formula: (end-systolic diameter–end-diastolic diameter)/end-systolic diameter, which has been demonstrated to be an alternative parameter for assessing fetal diastolic function [33]. In adults, several studies have found an association between increased ventricular filling pressure and increased LAV and EF, in which changes in its volume correlated with an increase in risk [34–38]. LAV may be more reliable in assessment of diastole than mitral Doppler [39]. It is a stable and reliable parameter that reflects the duration and severity of diastolic dysfunction. The study by Briguori et al. [40] in adults suggested that left ventricular

diastolic function could be better assessed through left atrial motion than through mitral flows in patients with hypertrophic cardiomyopathy. Later a similar study by Zalinski et al. [41] in fetuses of women with diabetes mellitus showed that left atrial shortening was decreased as compared with that in healthy fetuses. Further studies are needed to determine the relationship between LAV and EF and diastolic dysfunction in fetuses in pathological states.

Study limitations

There were several limitations to this study. First, it was a pilot study to apply the LAVT method to determine LAV in normal human fetuses. LAV data obtained through this method lack validation in in-vitro studies or animal experiments. Thus, to approximate the true LAV, more studies are necessary to further assess the accuracy of this method in the future. Second, phasic functions of the left atrium cannot be studied for a lack of guide of the fetal electrocardiogram. Third, there were several limiting factors for TLAVCs acquisition. An important limiting factor was a persistent unfavorable fetal position, which prevented the sonographers from acquiring the standard views, mainly the two-chamber view, which may potentially affect the accuracy of the measurements. Other limiting factors for the acquisition included low image resolution at young GA, abundant fetal movement, and numerous acoustic shadows.

CONCLUSION

This study presents reference ranges for indices of LAV for normal fetuses from 21 to 40 weeks of gestation. The growth curve of LAV of the normal human fetus is in line with that of the left ventricle. In our opinion, more studies are needed to assess to what extent measurements in fetuses in pathological states deviate from normal and whether these measurements can be of use in the prediction of fetal outcomes. Although there are still several factors limiting the application of this method, the LAVT method appears to be a feasible method to estimate fetal LAV and left atrial EF during the second half of gestation, suggesting its potential for assessing left ventricular diastolic function of fetal hearts, especially under pathological conditions in the mother or fetus.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

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