

Assessment of Left Atrial Phasic Volumes and Functions During Third Trimester of Healthy Pregnancy

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Abstract Background: Conception represents a physiological progression associated with adaptations in the structure, blood flow dynamics, and operational aspects of the cardiac response to temporary alternation in both preload and afterload. Ventricular volume and LA dimensions gradually and continuously increase due to increasing cardiac output and preload. The increased volume burden during the last trimester aggravates the possible cardiovascular disorders. Limited echocardiographic information exists on left atrium (LA) volume and function during the third trimester of standard conception among Iraqi women. **Aim:** To estimate the capacity and functionality of the left atrium throughout the last trimester of standard conception. **Methods:** This research was carried out on 75 normal gravid females (cases) and 75 nonpregnant females (control); women were given attention at Al-Furat Teaching Hospital from the 1 of April 2022 to the 30 of May 2023, the comprehensive 2D echocardiographic study had been done for each one of them. **Results:** Pregnant women category revealed a high noteworthy rise in left atrial maximum volume LA Max, left atrial minimum volume (LA Min) and pre-atrial volume (LA Pre- A) in contrast to nonpregnant women group (41.8 ± 11.50 vs. 25.16 ± 6.04 , $P < 0.0001$), (17.28 ± 7.76 vs. 11.77 ± 4.07 , $P < 0.0001$) and (8.69 ± 4.24 vs. 6.8 ± 2.93 , $P < 0.002$) respectively. As well, the study showed that in pregnant women group there is high significant increase in Left atrium reservoir capacity, Left atrium conduit role and LA booster duty 32.94 ± 9.57 vs. 18.38 ± 4.79 , $p < 0.0001$, (24.26 ± 9.06 vs. 13.41 ± 3.92 , $p < 0.0001$) (8.58 ± 4.66 vs. 4.98 ± 2.30 , $p < 0.0001$) contrasted with control. Additionally, the total emptying fraction%, LA Active ejection fraction % significantly higher in pregnant women than the control (0.79 ± 0.08 vs. 0.73 ± 0.09 , $p < 0.0001$), (0.49 ± 0.13 vs. 0.42 ± 0.13 , $p < 0.002$) while the LA Passive EF% had no significant difference between pregnant women (0.58 ± 0.14) about control (0.53 ± 0.10) ($P < 0.026$). **Conclusion:** In normal gravid females in the last trimester, there is an increase in LA volumes (LA maximum volume, LA minimum volume, and LA pre-A volumes) and enhancement in LA reservoir capacity, conduit role, and booster functions by using 2DE, which can quickly assess LA phasic volumes and function.

Key Words Left atrium, Left atrial phasic volumes, Third trimester pregnancy

1. Introduction

Atrium originates from Latin and explicitly denotes a central space within a Roman house. This area served as a pivotal room, providing access to several chambers connected to it [1]. The left atrium constitutes a component of the heart's four-chambers. It collects high oxygen-containing blood from the pulmonary circulation and propels it through the left ventricle, subsequently to the systemic vascular circulation [2]. The (LA) plays a vital role in the functioning of the cardiovascular system, which serves as a mechanical participant. It also serves as a stretchable storage chamber and facilitates left ventricular filling. It is also essential in managing intravascular volume by synthesizing atrial natriuretic peptide.

Even though LA diameter in the parasternal long-axis view is commonly utilized, it is stated that the LA volume proved to be a more forceful indicator for forecasting events than left atrial areas or diameters [3].

2. General Anatomical Characteristic of LA

The left atrium is situated close to the heart's base, a chamber with cuboidal shape; it holds the distinction of being the endmost posterior among all cardiac cavities. The upper left atrium's wall is near the connection point where the pulmonary trunk connects to the right pulmonary artery. The LA connects to the basal part of the left ventricle anteroinferiorly and the left at the atrioventricular valve. Furthermore, once

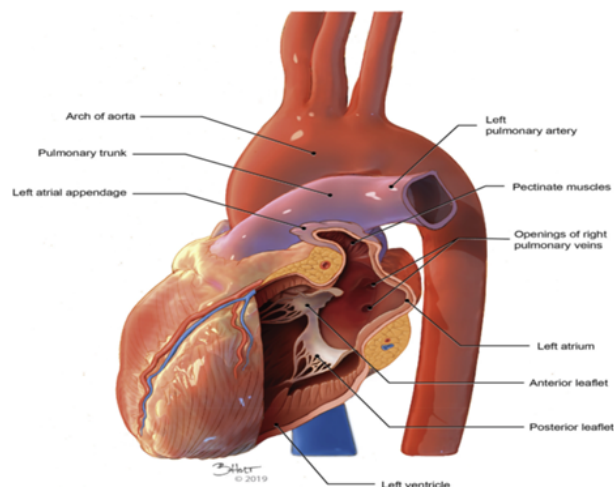


Figure 1: The characteristics of the left atrium are detailed in the figure created by Brandon Holt in 2019, shared under the CC-BY-NC-ND license. [4]

observed, the coronary sinus system is situated inferiorly and on the posterior aspect of the left atrium, filling the Atrioventricular septal groove [4]. Despite being smaller, the left atrium exhibits muscularity and Thickness greater than that of the right atrium [2]. The left atrial myocardium is penetrated by openings of pulmonary veins at its proximal end, laterally the left atrial appendixes, and the atrioventricular valve distally (Figure 1), [4]. Entirely through the wall, the thickness of the muscle layer of the left upper wall falls within the range of 3.5 to 6.5 millimeters, and the thickness of the lateral wall is estimated to range between 2.5 and 4.9 millimeters. The cardiac muscle fibers consist of single or multiple Sequential layers, exhibiting noticeable Variances in sectional thickness [5].

3. LA Function

The primary mechanical role of the left atrium (LA) is to facilitate and regulate the left ventricle (LV) filling with blood returning from the lungs. This is accomplished during LV systole as a storage for the inflow volume from pulmonary veins, as a conduit during early LV diastole transferring blood stored in the atrium, and from the pulmonary veins to the LV, and finally, as a booster pump that enhances LV end-diastolic filling [3]. Although LA assessment has been proven to be very useful in many cardiovascular diseases, the assessment of LA function is complex due to a variety of reasons, such as geometrical assumptions, as the LA shape is not as simple due to the presence of the LA appendage, pulmonary veins conflux, and the interatrial septum. Since LA varies during the cardiac cycle, temporal sampling is recommended when precise evaluations of dimensional changes are required. So no other imaging technique, except echocardiography, can be used as a gold standard for assessing the LA dynamic changes; even the cardiac magnetic resonance (CMR) is insufficient for assisting fast changes in LA dimensions,

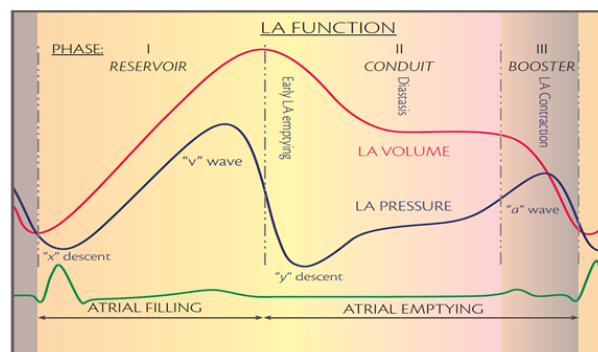


Figure 2: Left atrial function. Schema indicating the phases of LA function, volume, and pressure changes over the cardiac cycle [3]

especially when irregular and fast rhythms are present [3].

When the mitral valve (MV) is closed throughout (LV) systole and the phase of isovolumic relaxation, the left atrium acts as a distensible reservoir, accommodating blood flow from the pulmonary veins and storing elastic strength generated by systolic descent of the mitral annular plane as pressure. The elastic energy is returned throughout early LV diastole, facilitating early LV filling [3], [6]. Then, the LA functions as a conduit that starts with the opening of MV and concludes before the onset of LA contraction, facilitating passive emptying during the early phase of ventricular diastole and diastasis. Lastly, at end-diastole, the Left atrium is also a cardiac muscular pump (booster), which operates depending on its pre-load by the Frank-Starling mechanism aiding in the active emptying to maintain a sufficient left ventricular end-diastolic volume [3], [6]. Understanding these roles is critical for correctly determining phasic variations in dimensions and flow patterns into and out of the LA During cardiac pulsation in both normal and diseased hearts (Figure 2).

The strength accumulated by the LA throughout ventricular contraction is discharged upon the opening of mitral valve , considerably adding to Left ventricular stroke volume during left atrial reservoir stage. The conduit stage of LA encompasses the early Fullness of the left ventricle and diastasis period. The effectiveness of left atrium contractile phase contingent on factors as contractility ,intrinsic ,preload ,afterload as well as electromechanical coupling. Echocardiography has emerged as Proven non-invasive technique for Assessment of the triphasic nature of this physiological process [6].

During pregnancy, the heart undergoes morphological , hemodynamic , and functional adaptation as transient changes occur in both preload and afterload . The augmentation of volumetric load and reduction of peripheral resistance throughout conception have been extensively recorded in earlier publications [7], [8].

The escalation of the volume load during the third trimester exacerbates any underlying possible cardiovascular

condition. Ex-studies have shown alterations in left ventricular function during conception, with a particular focus on diastolic function. Anatomical and functional adaptations work as markers for left ventricular diastolic dysfunction [9]. Despite numerous publications on maternal heart adaptation during pregnancy [10], [11]. There is a notable gap in addressing Left atrial functions and its correlation with other cardiovascular adaptation findings [12].

4. Methods

The research participants were obtained from the Obstetrics and Gynecology Consultation clinic in Al-Furat Teaching Hospital at Al-Najaf Governorate; this collection spanned from the start of April 2022 till the end of March 2023. The research group involved 75 normal gravid women between 18-40 years old in the last trimester and 75 normal non-gravid females of a similar age range as a control group. Most women underwent complete evaluation, including systematic health history and examination to rule out other conditions such as clinical evidence or previous history of any Heart organic disorders, kidney impairment, thyroid gland disorder, marked anemia, diabetes mellitus, hypertensive disorder, taking long-term medication, or being a smoker. The height (cm) and weight (kg) are obtained sequentially using a tape measure and weight measuring device. Calculation of body mass index is carried out as Weight (kg) / Height (m²) for each one [13]. ECG and abdominal ultrasound were documented for the calculation of weeks of gestation. Every woman in this research provided their Agreement after being informed.

Echocardiographic Analysis

A complete 2DE was conducted in all female participants, utilizing a Vivid E9 ultrasound machine GE Healthcare, Horten, Norway provided by 2.5 MHz S5-1probe. ECG leads were positioned on the chest, and female participants were evaluated in the left lateral decubitus position; this positioning was adopted to bring the heart forward towards the chest wall and laterally aligned with the sternum in a room with subdued lighting adhering to the American society of echocardiography. LV diastolic measures were assessed from the apical 4-chamber imaging utilizing pulsed-wave Doppler at the mitral orifice; this encompassed measurements of early E as well as late A trans mitral speed of blood flow as well as Early-to-late velocity ratio E/A. The mean of Maximum early diastolic speeds at both the septal and lateral regions of the mitral annulus (E') was evaluated using pulsed-wave Doppler; additionally, the E/E' ratio was calculated to evaluate left Ventricular preload pressure [14].

LA Measurements

2D biplane method: The anterior-posterior diameter, measured by M-mode or 2D echocardiography, is disregarded as an accurate measure for the real Left Atrial Diameters. Consequently, the American Society of Echocardiography and the European Association of Echocardiography suggest

measuring Left atrial volumes utilizing an ellipsoid representation or Simpson's technique in both four-chamber and two-chamber apical visualization [6].

After tracing the LA cavity areas, the measurement software package automatically calculates the LA volume according to or using the area "length formula (Figure 3):

$$LeftatrialvolumemL = \frac{[0.85 \times A4Carea \times A2Carea]}{Length(15)}$$

Modified biplane Simpson's rule or area'length method

- 1) by using 2 orthogonal planes of the LA (usually A4C and A2C views)
- 2) Obtaining the best image quality, optimizing sector width and place focal zones distally for better lateral resolution in the far-field and increasing gain just to the point on which image drop-outs in the atrial walls have disappeared.
- 3) To achieve maximum LA size, avoid LA foreshortening (differences in length measured from the two orthogonal planes should be equal or less than 5mm).
- 4) Selecting adequate frames for measurement. End-systolic frame (just prior to the opening of mitral valve , T-wave termination on ECG) for maximum left atrial volume.
- 5) LA area border planimetry , the inferior border should be the mitral annular plane and endocardial contouring must specifically omit atrial appendage and pulmonary veins.
- 6) Long axis Left atrium : orthogonal to mitral valve annulus plane from its midpoint to upper edge of LA.

As small discrepancies are acceptable, the most common option is to average the lengths measurements obtained in the 4-chamber and 2-chamber imaging [15].

Left Atrium Passive Volumes Comprise (Figure 3)

- Maximal LA capacity LA max, attained from an end-systolic frame measured just Preceding to the onset of mitral valve opening in the final phase of systole.
- Minimum Left atrial capacity (LA min), gained from a frame at the end of diastole just preceding to closure of the mitral valve .
- Pre-atrial contraction volume (V=LApreA), gained from a frame just before to reopening of mitral valve as a consequence of LA Compression at the start of the P-wave on an electrocardiogram (ECG).

Left Atrium Active Capacity are

- Left atrium reservoir volume (LA max* LA min)
- Left atrium conduit volume (LV total stroke volume- LA reservoir volume)
- Left atrium passive emptying volume (LA max- LA pre A)

Left atrium contractile volume (LA pre A - LA min)

[6]

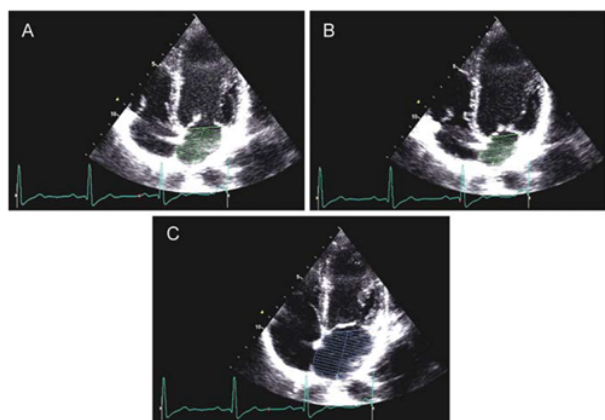


Figure 3: Pre-atrial compression volume (pre A) , assists at the start of the P-wave on an electrocardiogram (A); minimum LA volume (LA min), assists when mitral valve closes in end of diastole (B); and maximum LA volume (LA max), assists just prior to mitral valve opening in end-systole [6]

The Left Atrium Reservoir Function was Measured by: Left atrium (total emptying volume), determined as LA max LA min.

Left atrium conduct function was estimated by: Passive evacuation volume or (LA stroke volume) calculated as LA max LA pre-A.

Left atrium booster pump function was measured by: Active atrial stroke volume, determined as LA pre-A LA min.

Total emptying fraction (EF)= Total emptying volume /LA max.

Passive EF=Passive emptying volume / LA max.

Active EF= active emptying volume /pre-A [9].

Statistical Analysis

Conducting using SPSS 18. Data analyzed as per group I (total: n=75) compared with a control Group (total: n=75). Calculation of mean, standard deviation and standard error of mean was done. Study groups are compared using independent T test. Probability value P of < 0.05 deemed to be significant ($\alpha=0.05$)

5. The results

The Age, gender, height, and weight are variables that impact the volumes of the left atrium. [16], [17] and because the study population were matched by age and sex , thus, to account these possible changes, LA volumes were indexed to BSA. In our research , no differences have been identified between the indexed & original measures of all LA volumes after correcting for BSA.

SD: standard deviation, LA :left atrium, Max: maximum, Pre-A: pre- atrial , Min: minimum, EF: ejection fraction, E/A : E Maximum early diastolic transmitral flow speed / A Maximum late diastolic transmitral flow speed, EÂ´ Mean early diastolic velocities at mitral annulus.

Echocardiographic variable	Pregnant (n=75)	Control (n=75)	P value
	Mean±SD	Mean±SD	
LA Max	41.8 ± 11.50	25.16 ± 6.04	0.0001
LA Pre-A	17.28 ± 7.76	11.77 ± 4.07	0.0001
LA Min	8.69 ± 4.24	6.8 ± 2.93	0.002
LA reservoir function	32.94 ± 9.57	18.38 ± 4.79	0.0001
LA conduit function	24.26 ± 9.06	13.41 ± 3.92	0.0001
LA booster function	8.58 ± 4.66	4.98 ± 2.30	0.0001
Total emptying fraction	0.79 ± 0.08	0.73 ± 0.09	0.0001
Passive LA EF%	0.58 ± 0.14	0.53 ± 0.10	0.026
Active LA EF%	0.49 ± 0.13	0.42 ± 0.13	0.002
Mitral Valve E/A	1.25 ± 0.32	1.4 ± 0.4	0.036
E/EÂ´	6.93 ± 1.81	6.3 ± 1.2	0.01

Table 1: Shows LA volumes in pregnant and nonpregnant group of women

The current study presents the traditional echocardiographic data in Table 1. We noticed an expanded LA volume (Max, Min, and Pre-A) and increased LA reservoir, conduit, and booster function when evaluating pregnant women and control groups. The value of the LA emptying fraction significantly increased, as well as the LA active and passive ejection fraction in pregnant women. In addition, the mitral E/A ratio revealed significant differences between the two categories, and the mitral E/E ratio was also raised in the pregnant women group.

6. Discussion

The left atrium’s function is pivotal in maintaining optimal cardiac output. An elevation in left atrial volume might coincide with a Gradual decline in LA function, and both these factors May antedate the appearance of symptoms and potentially influence prognosis Negatively [18]. Furthermore, the Left atrium serves as a volume sensor, releasing natriuretic peptides when the atrial wall experiences stretch; this response leads to natriuresis, vasodilatation, and inhibition of the sympathetic nervous system and renin-angiotensin-aldosterone system [18].

It is well known that the total blood volume rises Markedly throughout conception, resulting in the enlargement of the LA volume; in normal conception, the left atrium undergoes remodeling to address special hemodynamic and metabolic requirements [19].

LA Reservoir Function

The left atrium serves t as a holding chamber, retaining the incoming blood from the vein of the pulmonary circulation and storing pressure as strength during the contraction of LV. The reservoir role of the left atrium is Resolute by the contraction and relaxation of its myocardium along with mitral annulus displacement during left ventricular systole [11]. In this research, the enhancement of the LA reservoir function occurred due to a dual effect; the reduction in LV compliance and the rise in heart rate negatively impacted LA emptying. The left atrium initiated a process of adaptive enlargement to ensure proper filling of the left ventricle and meet the escalating demands of cardiac output [11].

LA Conduit Function

The LA serves like a conduit, facilitating blood flow from the pulmonary circulation into the left ventricle during Left ventricular diastole. The conduit function of the left atrium is intricately linked to its reservoir function and is inherently connected to the LV relaxation and compliance [20].

However, the study results showed that the conduit function increased; these results differ from that of Song et al. [11], who found a decrease in the LA conduit function during pregnancy, maybe because the study also showed high E/A and E/ E' values that reveal good LV relaxation; the primary determinant of conduit function [21].

A Booster Pump Function

The primary role of the left atrium is to function as an active pump, ensuring the maintenance of LV filling during its systole. Booster function mirrors both the strength and timing of atrial contractility; additionally, the booster function is not solely reliant on the stretch resulting from atrial preload (LA pre-A) but also on (atrial afterload); this characteristic is reflected by the left ventricle end-diastolic pressure, in this study, enhanced LA booster function might be due to that The myocardial contractility of the left atrium responds to the increased left atrial preload according to the Frank-Starling mechanism [22]. This response remains in a compensating condition during a normal conception. The expansion of the LA and the rise in LA emptying fraction represent adjustable measures for maintaining normal LV filling pressures and resultantly LV stroke volume [23].

7. Conclusion

The demonstration that has been found is that the LA volume increases during pregnancy, and LA (reservoir, conduit, and booster pump) functions are enhanced during pregnancy. This most likely occurs as a compensatory response assists in maintaining cardiac output in pregnant women. Even if there are no comorbidities at the time of booking, cardiovascular alterations in pregnant women should be considered during their evaluation and care throughout the antenatal period.

Limitations of the research

Because most gravid females become fatigued during their echocardiographic examination, the examiner must act quickly to alleviate those prior to becoming fatigued. Furthermore, the study could not determine the patients' genuine baseline characteristics before their conception as the participants were chosen in their third trimester.

Acknowledgment

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Ethical Approval and Participant Consent

The research obtained informed consent from all participants, and the research design obtained approval from the Department of Physiology, Faculty of Medicine, University of Kufa (Department of Echocardiography), Al-Furat Teaching Hospital, Najaf, Iraq.

Abbreviation

left atrium ; EF :ejection fraction ;2DE : two -dimensional echocardiography , Max: maximum, Min: minimum; LV : left ventricle ;LAEF: left atrium emptying function, Pre-A : pre-atrial , SD: standard deviation, EF: ejection fraction, E/A : E" Peak velocity of the early diastolic transmitral wave. / A" Peak velocity of the late diastolic transmitral wave , E' the mean of peak early diastolic velocities at the septal and later l region of mitral annular.

Conflict of interest

The authors declare no conflict of interests.All authors read and approved final version of the paper.

Authors Contribution

All authors contributed equally in this paper.

References

- [1] Loukas, M., Youssef, P., Gielecki, J., Walocha, J., Natsis, K., & Tubbs, R. S. (2016). History of cardiac anatomy: a comprehensive review from the Egyptians to today. *Clinical Anatomy*, 29(3), 270-284.
- [2] Standring, S., Ellis, H., Healy, J., Johnson, D., Williams, A., Collins, P., & Wigley, C. (2005). *Gray's anatomy: the anatomical basis of clinical practice*. American journal of neuroradiology, 26(10), 2703.
- [3] Galiuto, L., Badano, L., Fox, K., Sicari, R., Zamorano, J. L. (2011). *The EAE Textbook of Echocardiography* . Oxford University Press Inc., New York.
- [4] Whiteman, S., Saker, E., Courant, V., Salandy, S., Gielecki, J., Zurada, A., Loukas, M. (2019). An anatomical review of the left atrium. *Translational Research in Anatomy*, 17 , 100052.
- [5] Ancona, R., Comenale Pinto, S., Caso, P., D'Andrea, A., Di Salvo, G., Arenga, F., ... & Calabrò, R. (2014). Left atrium by echocardiography in clinical practice: from conventional methods to new echocardiographic techniques. *The Scientific World Journal*, 2014. 451042.
- [6] Addo, V. N. (2010). Body mass index, weight gain during pregnancy. *Ghana Medical Journal*, 44 (2), 223.
- [7] Lang, R. M., Badano, L. P., Mor-Avi, V., Afzal, J., Armstrong, A., Ernande, L., ... & Voigt, J. U. (2015). Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *European Heart Journal-Cardiovascular Imaging*, 16(3), 233-271.
- [8] Todaro, M. C., Choudhuri, I., Belohlavek, M., Jahangir, A., Carerj, S., Oreto, L., & Khandheria, B. K. (2012). New echocardiographic techniques for evaluation of left atrial mechanics. *European Heart Journal-Cardiovascular Imaging*, 13(12), 973-984.
- [9] Kolovetsiou-Kreiner, V., Moertl, M. G., Papousek, I., Schmid-Zalaudek, K., Lang, U., Schlembach, D., ... & Lackner, H. K. (2018). Maternal cardiovascular and endothelial function from first trimester to postpartum. *PLoS One*, 13(5), e0197748.
- [10] Osman, M. W., Nath, M., Khalil, A., Webb, D. R., Robinson, T. G., & Mousa, H. A. (2017). Longitudinal study to assess changes in arterial stiffness and cardiac output parameters among low-risk pregnant women. *Pregnancy Hypertens*, 10 , 256-261.
- [11] Song, G., Liu, J., Ren, W., Qiao, W., Zhang, J., Zhan, Y., & Bi, W. (2015). Reversible changes of left atrial function during pregnancy assessed by two-dimensional speckle tracking echocardiography. *PLoS one*, 10(5), e0125347.

- [12] Melchiorre, K., Sharma, R., Thilaganathan, B. (2012). Cardiac structure and function in normal pregnancy. *Current Opinion in Obstetrics and Gynecology*, 24 , 413-421.
- [13] Ouzounian, J. G., Elkayam, U. (2012). Physiologic changes during normal pregnancy and delivery. *Cardiology Clinics*, 30 , 317-329.
- [14] Tasar, O., Kocabay, G., Karagoz, A., Kalayci Karabay, A., Karabay, C. Y., Kalkan, S., & Kirma, C. (2019). Evaluation of Left Atrial Functions by 2-dimensional Speckle-Tracking Echocardiography During Healthy Pregnancy. *Journal of Ultrasound in Medicine*, 38(11), 2981-2988.
- [15] Kühn, H. P., Schreckenber, M., Rulands, D., Katoh, M., Schäfer, W., Schummers, G., ... & Franke, A. (2004). High-resolution transthoracic real-time three-dimensional echocardiography: quantitation of cardiac volumes and function using semi-automatic border detection and comparison with cardiac magnetic resonance imaging. *Journal of the American College of Cardiology*, 43(11), 2083-2090.
- [16] Eshoo, S., Ross, D. L., & Thomas, L. (2009). Impact of mild hypertension on left atrial size and function. *Circulation: Cardiovascular Imaging*, 2(2), 93-99.
- [17] van Grootel, R. W., Strachinaru, M., Menting, M. E., McGhie, J., Roos Hesselink, J. W., & van den Bosch, A. E. (2018). In depth echocardiographic analysis of left atrial function in healthy adults using speckle tracking echocardiography and volumetric analysis. *Echocardiography*, 35(12), 1956-1965.
- [18] Kurt, M., Wang, J., Torre-Amione, G., & Nagueh, S. F. (2009). Left atrial function in diastolic heart failure. *Circulation: Cardiovascular Imaging*, 2(1), 10-15.
- [19] Ye, X., Li, Z., Li, Y., Cai, Q., Sun, L., Zhu, W., ... & Lu, X. (2021). Reduced mechanical function of the left atrial predicts adverse outcome in pregnant women with clustering of metabolic risk factors. *BMC Cardiovascular Disorders*, 21(1), 1-9.
- [20] Okamoto, K., Takeuchi, M., Nakai, H., Nishikage, T., Salgo, I. S., Husson, S., ... & Lang, R. M. (2009). Effects of aging on left atrial function assessed by two-dimensional speckle tracking echocardiography. *Journal of the American Society of Echocardiography*, 22(1), 70-75.
- [21] Andersen, O. S., Smiseth, O. A., Dokainish, H., Abudiyab, M. M., Schutt, R. C., Kumar, A., ... & Nagueh, S. F. (2017). Estimating left ventricular filling pressure by echocardiography. *Journal of the American College of Cardiology*, 69(15), 1937-1948.
- [22] Anwar, A. M., Geleijnse, M. L., Soliman, O. I., Nemes, A., & ten Cate, F. J. (2007). Left atrial Frank-Starling law assessed by real-time, three-dimensional echocardiographic left atrial volume changes. *Heart (British Cardiac Society)*, 93(11), 1393-1397.
- [23] Matsuda, Y., Toma, Y., Ogawa, H., Matsuzaki, M., Katayama, K., Fujii, T., ... & Kusukawa, R. (1983). Importance of left atrial function in patients with myocardial infarction. *Circulation*, 67(3), 566-571.