

Impact of Menopause on Left Atrial Mechanics and Left Atrioventricular Coupling: The Role of Sex Hormones and Cardiovascular Remodeling

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Abstract:

Background: Menopause is associated with an increased cardiovascular risk that cannot be explained by aging and conventional risk factors alone. The abrupt decline in estradiol, relative androgen predominance, and accompanying vascular and myocardial changes may adversely affect left atrial (LA) function and left atrioventricular coupling. This review summarizes current evidence on LA mechanics, available imaging methods, and menopause-related cardiac remodeling. LA strain, assessed mainly by two-dimensional speckle-tracking echocardiography, quantifies reservoir, conduit, and booster-pump function and may detect subclinical dysfunction before LA enlargement or a reduction in left ventricular ejection fraction becomes apparent. Cardiac magnetic resonance-derived left atrioventricular coupling index provides complementary information on the relationship between LA and left ventricular volumes. Evidence indicates that postmenopausal women demonstrate greater concentric left ventricular remodeling, larger LA size, impaired diastolic function, reduced longitudinal LA deformation, and increased atrial stiffness. These abnormalities become more pronounced with longer time since menopause and lower estradiol levels. Higher testosterone-to-estradiol ratios have also been associated with impaired atrioventricular coupling. Importantly, abnormal LA mechanics and coupling predict atrial fibrillation, heart failure, coronary events, and cardiovascular mortality. Assessment of LA strain and atrioventricular coupling may therefore improve early risk identification and guide preventive strategies in peri- and postmenopausal women.

Keywords: menopause; left atrial strain; estradiol; speckle-tracking echocardiography; cardiovascular remodeling.

Introduction:

2D Speckle Tracking Echocardiography (STE) is a post-processing ultrasound technique that evaluates myocardial mechanics. By automatically tracking natural grayscale acoustic markers ("speckles") from frame to frame, it allows cardiologists to quantify heart wall deformation, providing critical diagnostic data beyond standard ejection fraction.(1)

Due to its accessibility and reliability, STE is often the first choice for evaluating LA function and morphology. However, analyzing LA deformation with STE is more complex than analyzing the left ventricle due to the LA's thin wall, mobile septum, and complex geometry. Moreover, when using a transthoracic approach, the LA's position in the far field can make achieving optimal signal quality and resolution more challenging.(2)

Two-dimensional speckle tracking echocardiography (2D-STE) is a novel technique and the results are based on the deformation of the myocardium. Recently, studies have found that 2D-STE can be used in clinical practice to diagnose coronary heart disease in a specific population with acute myocardial infarction, angina pectoris, and chronic coronary heart disease, especially in outpatient departments. With 2D-STE, cardiologists can implement

timely interventional strategies in patients with non-ST-segment elevation myocardial infarction. 2D-STE has an extensive application value in clinical outpatient management, whether for screening patients or for evaluating postoperative rehabilitation.(3)

2D-STE is convenient, cost effective, and readily available compared with exercise electrocardiograph (ECG), cardiovascular magnetic resonance (CMR), and angiography. The latest guideline on non-ST-segment elevation acute coronary syndromes (NSTEMI-ACS) suggests that using GLPS might improve the diagnostic value of conventional echocardiography. This guideline does not have sufficient standardizations to recommend the routine use of 2D-STE in all patients with CAD. Thus, this study aimed to investigate the diagnostic value of 2D-STE for coronary heart disease in a large population of patients who underwent angiography. Our focus was to provide more evidence of the clinical application of 2D-STE in patients suspected of having coronary artery disease.(4)

❖ Assessment of left atrial strain

Assessment of left atrial (LA) strain is an advanced, non-invasive echocardiographic technique used to measure myocardial deformation. It evaluates subtle LA dysfunction before structural or volumetric changes occur. It is primarily assessed via 2D Speckle-Tracking Echocardiography (STE), but can also be evaluated using Cardiac Magnetic Resonance (CMR) imaging.(5)

Left atrial strain assessment provides a detailed picture of LA function throughout the cardiac cycle. It analyzes the three phases of LA activity: reservoir (LA filling by the pulmonary veins during ventricular systole), conduit (passive ventricular filling during early diastole), and booster-pump (active ventricular filling during late diastole).(6)

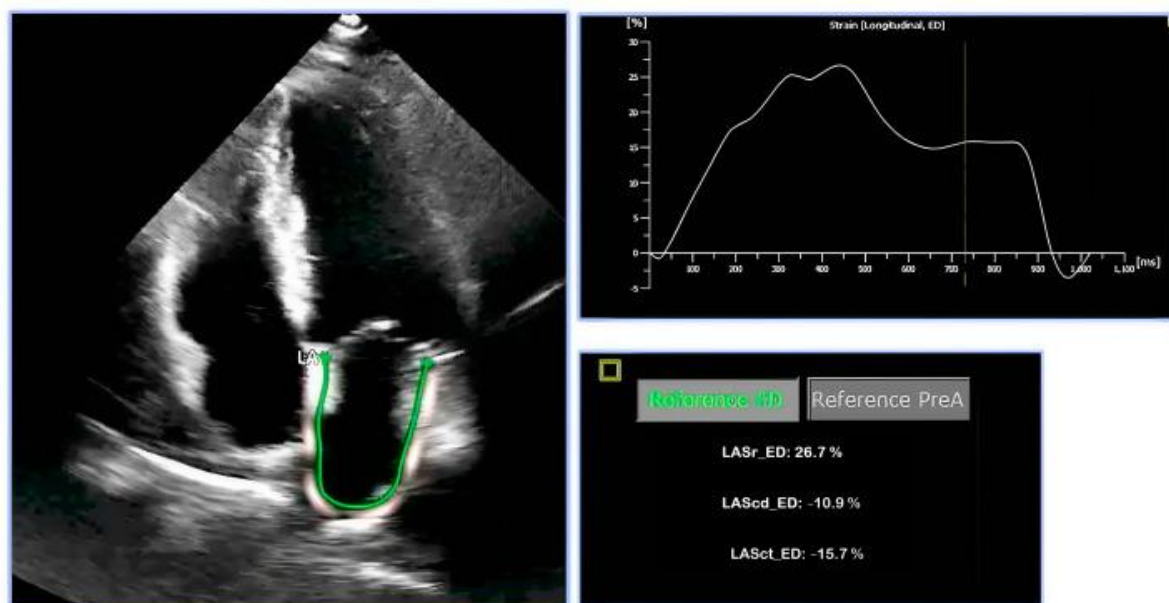


Figure 1. Left atrial strain. The figure shows the different phases of LAS. In the apical four-chamber, begin tracing at the endocardial border of the mitral annulus, follow the LA endocardial border, extending across the pulmonary veins, and/or the orifices of the LA appendage, up to the opposite mitral annulus side. Note, the left atrium is in the far field and, therefore, has reduced image resolution, making it hard to detect speckles. Therefore, we primarily perform contour detection between the blood (black) and the wall (white), followed by calculating length changes. ROI width of 3 mm is recommended, though adjustments should be made to avoid including the pericardium.

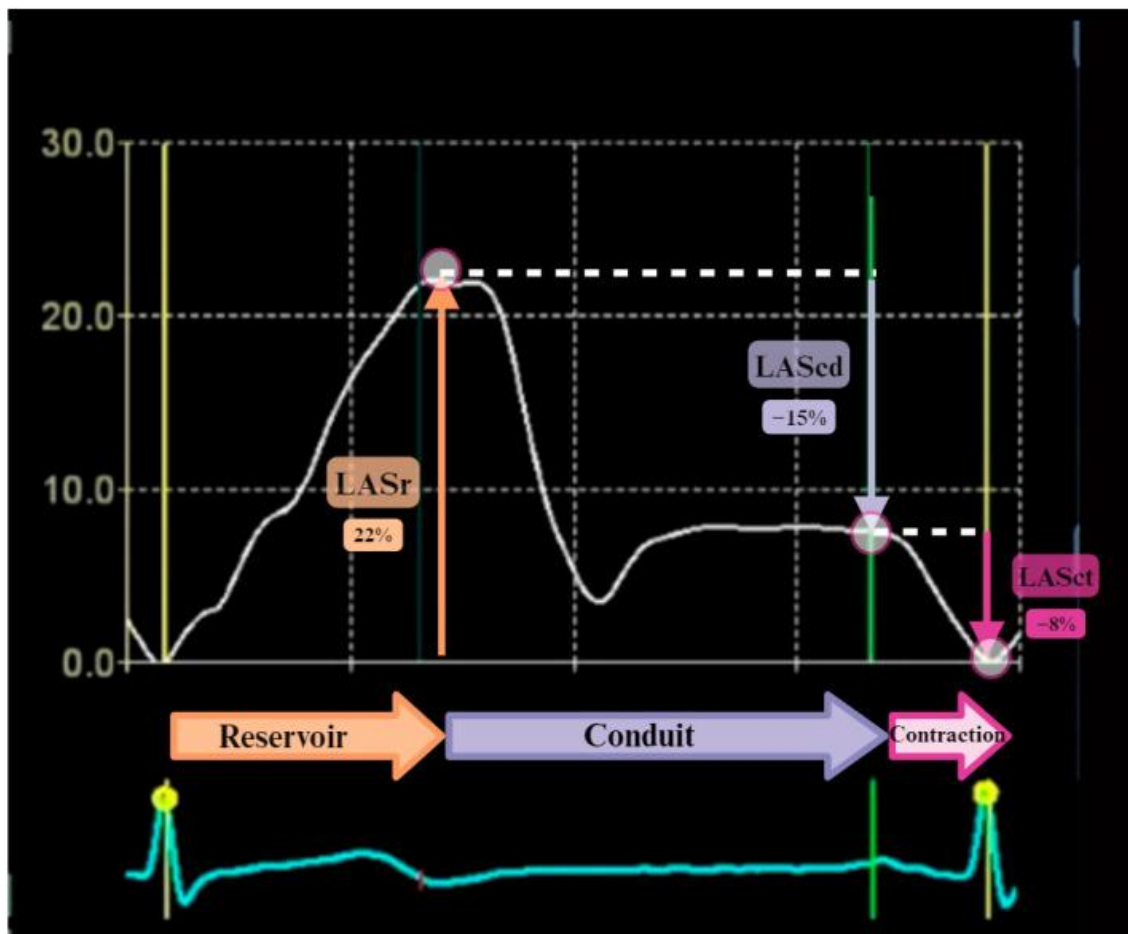


Figure 2. Zero baseline, here defined as the end of diastole. Reservoir—end-diastole to peak (positive value—

LA getting bigger), so LV reservoir function represents LA relaxation and compliance, modulated by LV systolic function through the descent of the LV base. Conduit = value from the peak to the pre-contraction phase (negative value); LA conduit function is reliant on LV diastolic function, including both suction force dependent on LV relaxation and LV chamber stiffness. Contraction = pre-contraction point to baseline (negative value) LA booster function is based on intrinsic LA contractility and LV end-diastolic compliance and pressure.

While LA volume assessment is widely recommended by scientific guidelines and represents a traditional marker for LA structural impairment, recognizing the dynamic nature of LA function through LAS assessment is increasingly seen as a more sensitive indicator of cardiovascular diseases. Although STE is often the initial modality for analyzing LAS and function, other advanced imaging techniques, such as CMR and CCTA, can also be useful in volumetric and functional analysis of the LA, although the measurements obtained from these different methods may differ.(7)

❖ Evaluation of LA function by LA strain

Trans-mitral peak A wave velocity, its velocity time integral and atrial fraction are well described measures of LA contractile function. The LA ejection force, based on Newtonian principles, incorporates peak A velocity and was used as a marker of LA function. Subsequently, tissue Doppler derived A' velocity was utilised as a less load dependent measure of LA contractile function, demonstrating good correlation with traditional Doppler and LA volumetric measurements. Colour tissue Doppler analysis was able to evaluate segmental LA function, demonstrating temporal changes with improved LA function following cardioversion. However, using these measures mandates the presence of sinus rhythm (SR). The LA function index (LAFI) was derived to evaluate LA function even in atrial fibrillation (AF). Additionally, volumetric measures including the LA ejection fraction (LAEF) and LA expansion index (LAEI) have been utilised, both in SR and AF. (8)

More recently, strain analysis has been utilised for evaluation of LA function. Strain evaluates myocardial deformation while strain rate examines the rate of change in strain, and can be measured throughout the cardiac cycle, thereby enabling the evaluation of LA reservoir function (in systole) and conduit and contractile function (in diastole) (9).

Strain and strain rate imaging of the LA

Strain and strain-rate imaging have several advantages over conventional echocardiography in evaluation of LA function. Firstly, strain imaging is not evaluated relative to the transducer position, thus allowing discrimination between active and passive myocardial tissue movement (. Strain parameters are relatively independent of tethering effects and is less load dependent compared to traditional parameters of LA function. Additionally, strain and strain rate parameters permit evaluation of phasic atrial function throughout the cardiac cycle. There are as yet no validated strain algorithms that have been developed exclusively for evaluation of LA function. However, several studies have utilised strain software that was developed for the left ventricle, with adjustments to the width of the 'region of interest '(ROI) to evaluate LA strain (10).

LA strain measurements can be obtained by tissue Doppler imaging (TDI), two dimensional (2D) speckle tracking echocardiography (STE) and velocity vector imaging (VVI). For the latter two techniques, longitudinal strain and strain rate curves are generated for each of six atrial segments, obtained from the apical four and two chamber views. Heterogeneous segmental deformation of the LA has also been observed, with higher values noted in the regions adjacent to the mitral annulus (11).

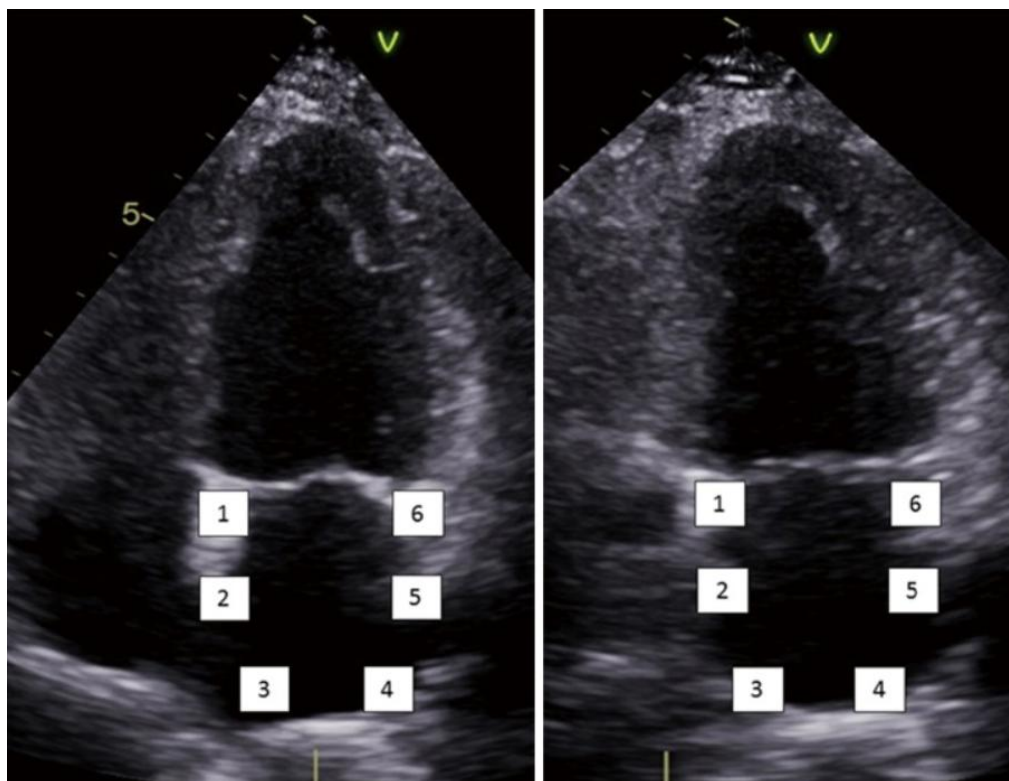


Figure 3 Apical four and two chamber six LA segments. LA, left atrial.

In the reservoir phase, as the LA fills and stretches, there is positive atrial strain that reaches its peak in systole at the end of LA filling, prior to opening of the mitral valve. Following this, passive LA emptying ensues with opening of the mitral valve resulting in decreased atrial strain with negative deflection of the strain curve up to a plateau period which is analogous to diastasis. A second deflection in the strain curve is then observed corresponding to atrial systole. Peak atrial longitudinal strain (PALS) or LA systolic strain is measured at the end of the reservoir phase. Peak atrial contraction strain (PACS) or late diastolic strain, is measured following the P wave and corresponds to active atrial contraction.(12)

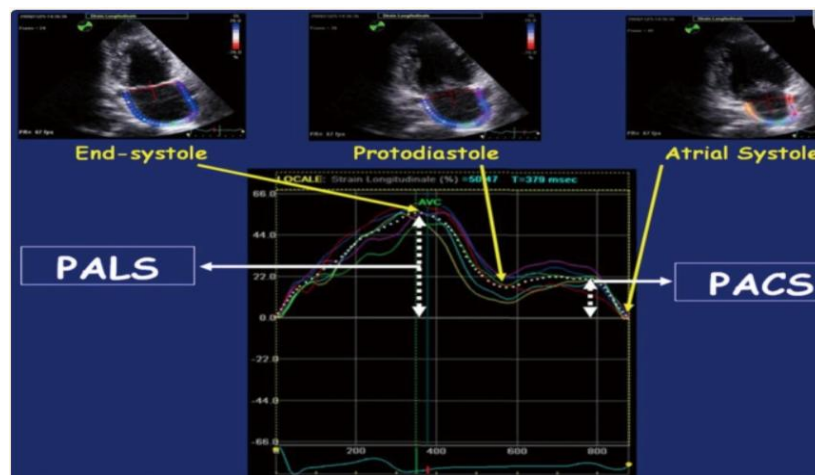


Figure 4 Peak atrial longitudinal strain (PALS) and peak atrial contraction strain (PACS).

LA strain curves have two patterns that differ based on the time in the cardiac cycle from which the software processing begins i.e., either at the onset of the P wave (atrial cycle/diastolic gating) or the onset of the QRS complex (ventricular cycle/systolic gating). If the strain processing begins at onset of QRS, ventricular end diastole is the zero reference and peak positive longitudinal strain corresponds to atrial reservoir function, strain during early diastole reflects atrial conduit function and strain during late diastole corresponds to atrial contractile function. Conversely, if software processing begins at onset of P wave, atrial end diastole becomes the zero reference and the first negative peak strain represents the atrial contractile function, positive peak strain corresponds to conduit function, and their sum (strain total) represents reservoir function. Strain rate in ventricular systole (S sr), early diastole (E sr) and late diastole (A sr) correspond to reservoir, conduit, and booster pump functions in both methods (13).

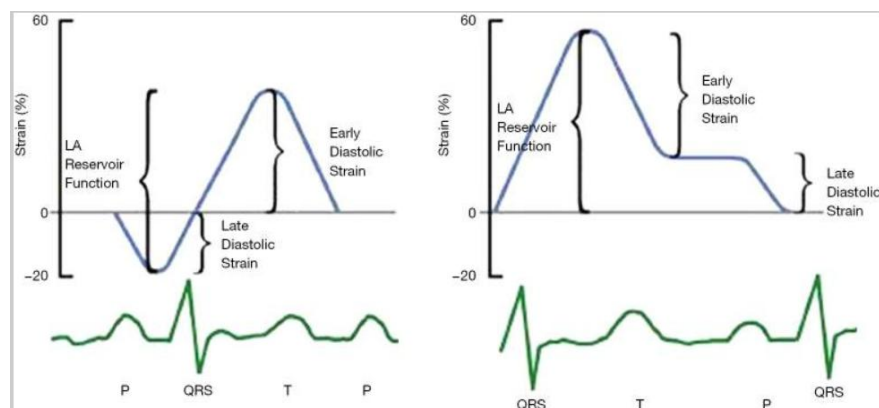


Figure 5 Strain trace based on choice of electrocardiographic gating; electrocardiographic P wave used on the left and QRS complex used on the right. Modified from Hoit et al. Left panel: P wave (atrial end diastole) used as zero reference point whereby first negative peak strain represents the atrial contractile function, positive peak strain corresponds to conduit function, and their sum (strain total) represents reservoir function. Right panel: QRS complex (ventricular end diastole) used as zero reference point whereby peak positive longitudinal strain corresponds to atrial reservoir function, strain during early diastole reflects atrial conduit function and strain during late diastole corresponds to atrial contractile function. LA, left atrial.

LA strain by 2D STE

STE is a newer echocardiographic technique for strain and strain rate analyses that tracks 'speckles' or natural acoustic markers in the 2D ultrasound image. The geometric shift of each speckle position is traced throughout the cardiac cycle (14).

STE strain is increasingly applied in the study of LA mechanics. Apical four and two chamber view images of the LA are obtained using conventional 2 dimensional echocardiography, at relatively high frame rates (60–80 fps). The LA endocardium is traced in both four and two chamber views and the ROI adjusted to the thinner wall of the atrium. In regions of discontinuities of the LA wall, such as areas corresponding to pulmonary veins and LA appendage, extrapolation of the LA endocardial and epicardial surfaces at the junction of these structures are performed to obtain the ROI. The ROI is divided into six segments and the total of 12 segments is analysed with the software generating the individual segmental longitudinal strain curves together with global strain in each view (15).

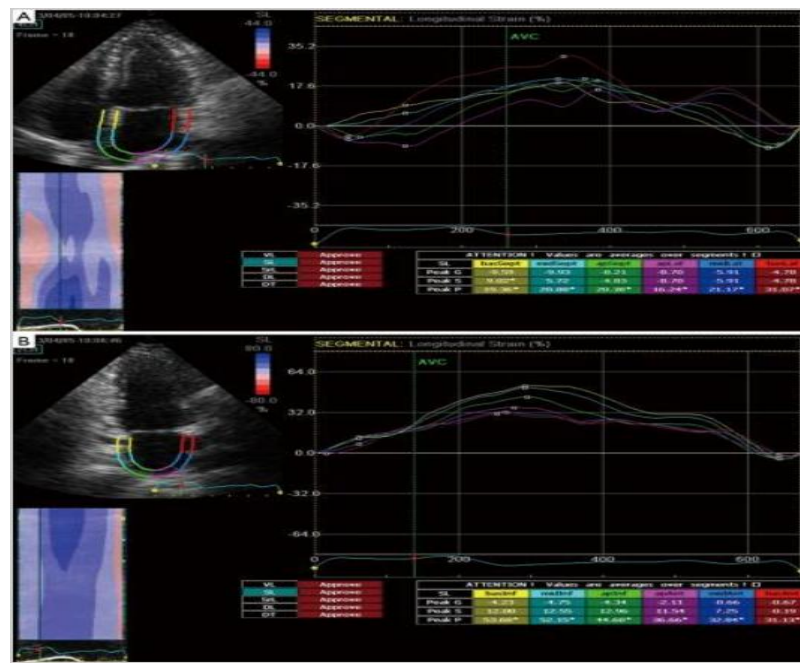


Figure 6 2D strain by speckle tracking echocardiography demonstrating segmental and global LA strain from the apical (A) four and (B) two chamber views. LA, left atria.

The feasibility and reproducibility of STE for the study of LA mechanics have been validated in several studies, and can be obtained in ~90% of cases. The major limitation is the necessity for adequate 2 dimensional image quality and acquisition at a relatively high frame rate. Though its utility is presently still limited to research settings (16).

LA strain by TDI

TDI depicts myocardial motion (measured as tissue velocity) at specific locations in the heart. Integration of velocity over time yields displacement or the absolute distance moved by that point.

Tissue-Doppler LA strain and strain rate are measured offline from colour tissue Doppler images of the atria obtained in the apical four and two chamber views, at high frame rates (>100 fps). A narrow sample volume (9 mm × 1 mm) is selected due to the thin atrial walls, as compared with the sample volume used for LV strain measurements (9 mm × 9 mm). The sample volume is placed superiorly in each of the four LA walls; septal and lateral walls in the apical four chamber view and the inferior and anterior walls in the apical two chamber view. The sample volume is then tracked frame by frame, within this position in the LA wall, to prevent sampling of blood pool. The superior location in the LA walls is selected to avoid interference from mitral annular motion. Peak LA systolic strain was measured by adjusting the electrocardiogram gating to the start of the QRS complex (systolic gating). Atrial strain rate was measured in S sr, E sr and A sr.(17)

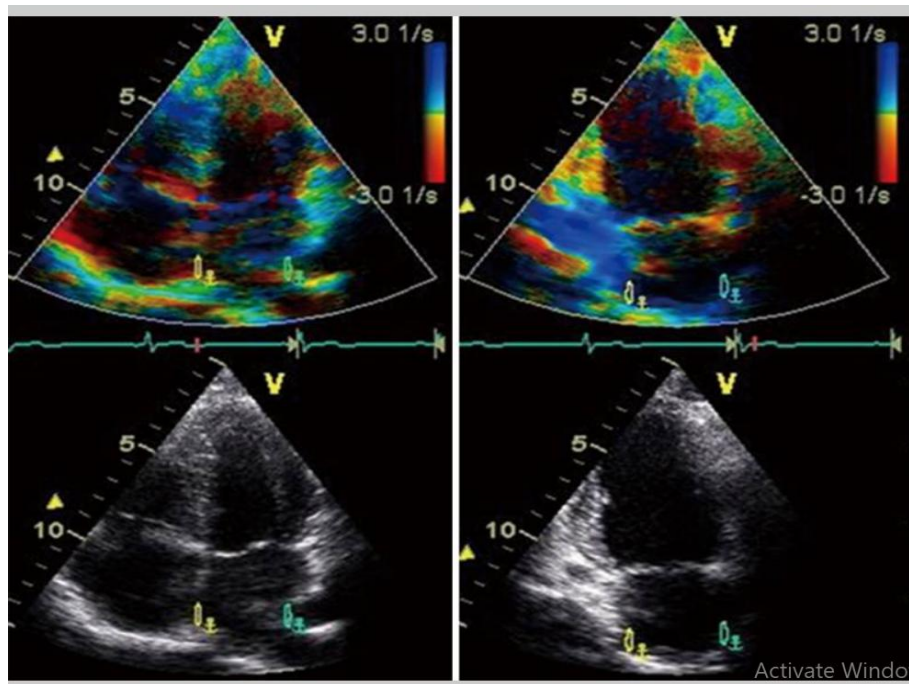


Figure 7 Peak systolic strain measured by ECG gating to the start of the QRS complex (systolic gating).

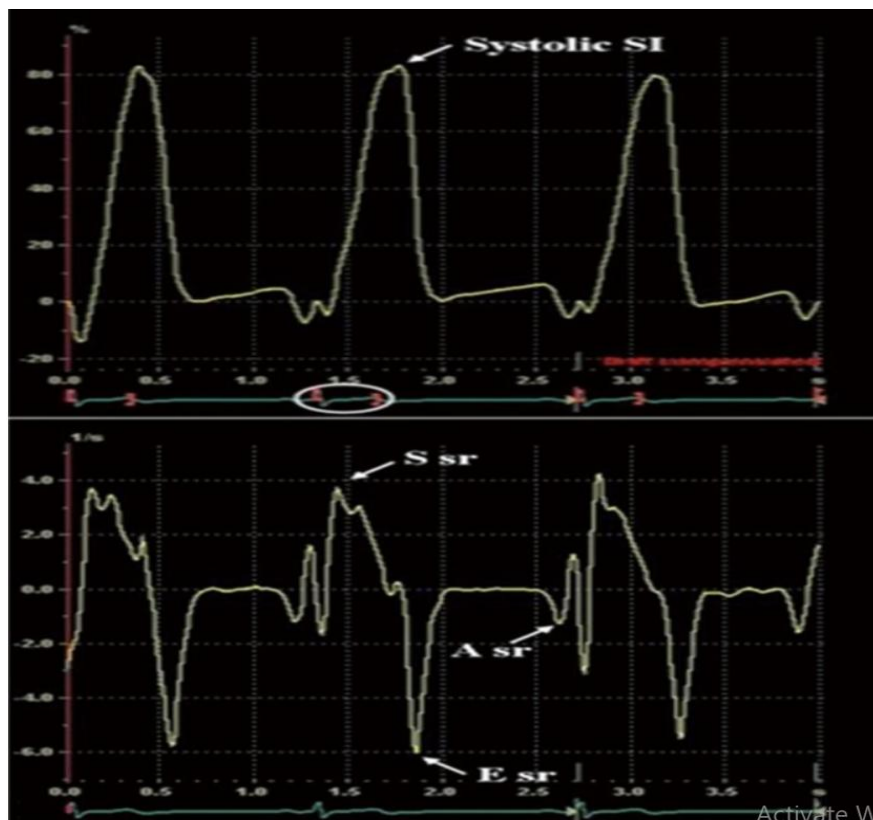


Figure 8 Atrial strain rate measured in systole (S sr), early (E sr) and late diastole (A sr).

From a physiological precept, healthy ageing is associated with alterations in LV systolic and diastolic strain, with corresponding changes in atrial strain. Doppler LA strain parameters demonstrate age related changes earlier than corresponding volumetric measurements of phasic LA function (18).

Tissue Doppler assessment of atrial strain has been utilised in a variety of clinical settings to quantitate atrial function, remodelling and changes in phasic atrial function. Evaluations have included patients with hypertension, hypertrophic cardiomyopathy, Fabry disease, atrial septal defects, valvular stenosis and AF (19).

TDI LA strain also has demonstrated prognostic value. Decreased LA systolic strain has been associated with increased LV end-diastolic pressure and is thus, a predictor of diastolic HF. LA TDI strain has also been shown to be an important predictor of maintenance of SR following both cardioversion and ablation for AF. In the only outcome based study using LA TDI strain, Paraskevaidis et al. showed that total TDI atrial strain in patients with hypertrophic cardiomyopathy was the strongest predictor of 12-month outcomes (20).

More recently TDI LA strain has been used to demonstrate reduced reservoir and conduit phasic function with preserved active contractile function in patients with metabolic syndrome. The use of tissue Doppler techniques in this cohort may have been of particular importance in the setting of potential suboptimal 2D image quality. (21).

LA strain by VVI

VVI is a novel echocardiographic method that combines speckle tracking and endocardial border detection. Similar to 2D STE strain imaging, VVI is angle independent but has additional advantages of simpler and faster tracking/processing times compared to conventional STE with the use of a continuously self-updating software and requires only a single frame tracing of the endocardial border (22).

With VVI analysis, 2D images of apical four and two chamber views are obtained with recommended frame rates between 70–100 Hz. The endocardium of the LA is manually traced in the four and two chamber views and velocity vectors are generated in cine loop format. The ROI is delineated and tracked. The displacement of LA endocardial pixels of the ROI and the velocity of deformation in every frame with the elongation or shortening of myocardium throughout the cardiac cycle, are the strain and SR measures which are calculated automatically. Special reference settings are applied, including valve annulus, chamber borders and tissue motion. (23)

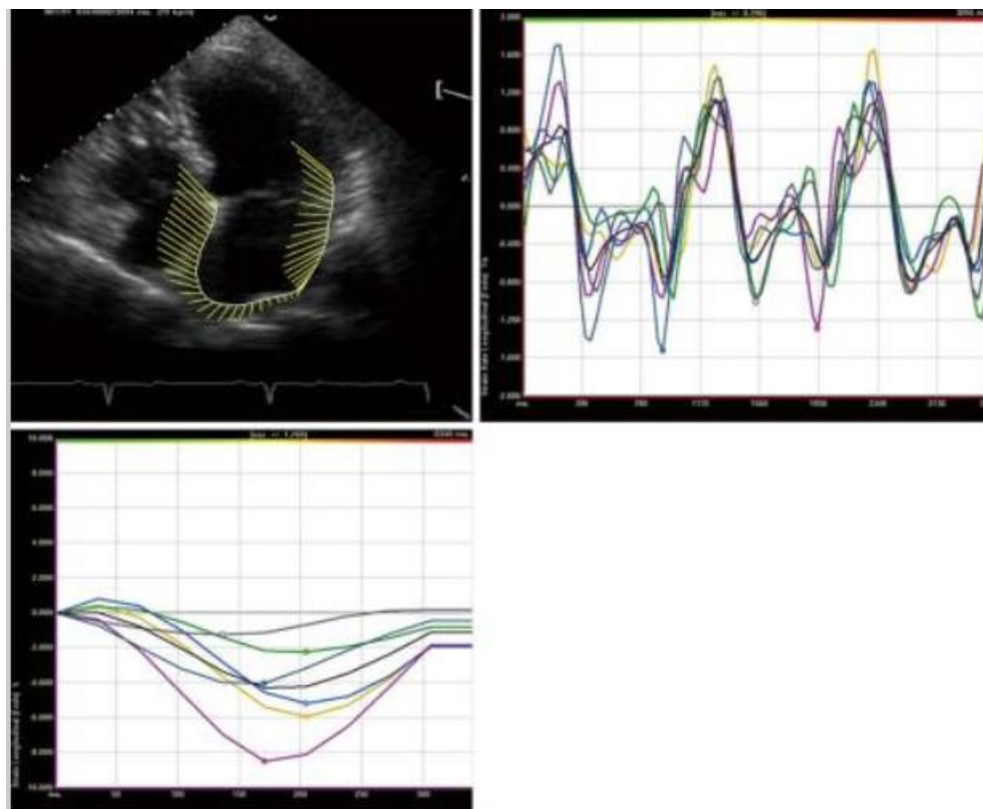


Figure 9 Velocity vector imaging.

VVI has been shown to be feasible and less time consuming in assessing LA volumes and function. In a study by Valocik et al. retrospectively assessing 100 transthoracic echocardiograms, LA volumes derived from VVI time volume curves had a good correlation with conventional LA volume assessment. A moderate level of correlation was noted with respect to LAEF. VVI led to a 62% reduction in measurement time in comparison to conventional 2D assessment. These findings were corroborated by Motoki et al. in a separate study involving 127 patients with AF. Measurement of LA strain and SR by VVI and 2D STE was noted to be feasible in a large proportion of patients with comparable strain and strain rate measurements using the two techniques (24).

LA strain assessed by VVI has shown clinical utility in patients with HF. Esmailzadeh et al. demonstrated that LA strain by VVI was significantly lower in patients with HFrEF compared to healthy subjects in a study involving 35 patients with LVEF <35% in SR. On multivariable analysis of diastolic parameters, a significant inverse relationship was identified between pulmonary arterial pressure and LA strain suggesting that systolic pulmonary artery pressure in HFrEF may be related to LA contractile dysfunction (25).

❖ Left atrial mechanics in pre-and post-menopausal women

Regarding the association between sex hormone levels and heart structure, recent studies have shown that higher free testosterone and lower SHBG levels are associated with greater LV mass and an increased LV mass-volume-ratio (concentric remodeling), higher endothelial dysfunction assessed using brachial artery flow-mediated dilation, higher LV diastolic dysfunction, and greater coronary artery calcium score progression. However, total testosterone and estradiol levels have not been associated with LV structure. Despite the contradictory outcomes of prospective studies that have assessed the plausible pathological pathways that link endogenous sex hormones and clinical CVD events, the MESA has recently shown that in post-menopausal women, a higher total testosterone level and a lower estradiol level are associated with an increased risk of CVD. However, the study also found that free testosterone and SHBG levels are not prognosticators of CVD. Together, these results suggest that total testosterone and estradiol levels influence CVD risk via mechanisms other than modification of LV structure.(26)

According to pezel et al., (9) a higher LACI value was significantly associated with a higher DHEA level, a higher total testosterone level, a lower estradiol level, and thus a higher total testosterone/estradiol ratio. Based on these results, we hypothesize that these sex hormones influence the left atrioventricular coupling function. Indeed, estradiol can downregulate angiotensin receptors, improve vascular endothelium function, protect against vascular injury, and inhibit adverse LV remodeling processes. (27)

In contrast, testosterone can increase platelet aggregation via upregulation of thromboxane and induce vasoconstriction. The effect of DHEA on CVD has not yet been defined. It was hypothesized that lower DHEA levels may be associated with an increased risk of cardiovascular events; however, this association has been disproved by numerous studies, particularly those conducted with elderly women. Therefore, in addition to these reported mechanisms by which estradiol and testosterone may play a prognostic role for peri- and post-menopausal women, the current findings suggest that the abrupt loss of estradiol at menopause and the potential increase in total testosterone may be significant contributors to left atrioventricular coupling. Moreover, the LACI was not associated with free testosterone and SHBG levels in this study, which supports the hypothesis that total testosterone and estradiol influence CVD risk through effects on left atrioventricular coupling and not just the modification of LV structure.(28)

Because the LACI is an independent prognosticator of cardiovascular events, even after adjusting for the total testosterone/estradiol ratio, the association between the LACI and both the total testosterone and estradiol levels supports the hypothesis that these hormones impact left atrioventricular coupling. Therefore, all these findings emphasize the complexity of the female hormonal system during the peri- and post-menopausal states; there are hormones acting independently and in combination. The findings suggest that the abrupt modification of sex hormone levels during menopause could critically influence left atrioventricular coupling, thus explaining the increase in cardiovascular events in older women. Beyond menopausal status and sex hormone levels, the LACI may help identify women who have an increased CVD risk and who may benefit from additional risk-reducing strategies.(29)

Female menopause and decreasing estradiol levels were associated with greater LV/LA remodeling coupled with declines in LV longitudinal and LA deformation. These structural and functional changes were accentuated with increasing years of menopause, independent of age and cardiovascular risk factors. Furthermore, among post-menopausal women, declining atrioventricular mechanics were independently associated with clinical outcomes. Collectively, these data contribute to our understanding of sex differences in HF and the predominance of postmenopausal women among patients with HFpEF.(30)

Our findings of smaller LV dimensions, greater LV sphericity and concentricity, larger LA size and worse LV diastolic function despite better LV systolic function in women compared to men are consistent with previous studies. Our results extend prior data by showing that independent of age and cardiovascular risk factors, female menopause is associated with greater LV and LA structural remodeling in tandem with subtle declines in LV and LA longitudinal deformation, despite preserved LV EF. Of note, while LV longitudinal function declined, LV torsional function increased in post-menopausal women. Torsion has shown to preserve global LV pump function (LVEF) by mechanically increasing the wringing motion of the heart and mechanistically favoring more efficient O₂ and energy utilization.(31)

The synergistic effects of a smaller LV size (dimensions and volumes), shorter LV long axis length and potentially greater LV sphericity in women could contribute to enhanced LV torsion by having more horizontally oriented oblique myocardial fibers between the subendocardium and subepicardium. This, (1) generates a greater net angle difference, which favors increased torsion (lever-arm theory) and (2) enhances shearing of subendocardial fibers toward the LV cavity during contraction, which promotes LV wall thickening. Our study further adds that post-menopausal women exhibit lower longitudinal atrial mechanics (15% PALS reduction) and increased atrial stiffness (40% increase), consistent with the known predisposition of elderly women to LV diastolic dysfunction despite preserved LVEF and atrial fibrillation.(32)

In a large multi-ethnic study population of pre-menopausal and post-menopausal women who were free of clinical CVD at baseline, a higher LACI (measured using CMR imaging) was associated with a higher risk of incident AF, HF, CHD death, and hard CVD during a 13-year average follow-up and this association did not vary by menopause status. Beyond menopausal status and HT use, the addition of the LACI to risk prediction models for these outcomes showed improvements in model discrimination and reclassification of cardiovascular event risks.(33)

Women have better LV systolic function, greater LV sphericity and torsion, as well as better LA mechanics but poorer LV diastolic function compared to men. Female menopause is associated with greater LV/LA remodeling coupled with declines in LV longitudinal and LA function independent of age and cardiovascular risk factors. The accentuation of these structural and function changes with increasing years of menopause and lower levels of estradiol, along with their independent prognostic value in post-menopausal women, may contribute to our understanding of sex differences in heart failure.(34)

References:

1. Colla J, Martin J, Eilbert W, Wishnoff M. Bedside Use of Speckle Tracking Echocardiography in the Emergency Department to Identify Acute Myocardial Infarction. *J Emerg Med*. 2019 May;56(5):530–5. doi:10.1016/j.jemermed.2019.01.014 PubMed PMID: 30853187.
2. Javadi N, Bismee NN, Abbas MT, Scalia IG, Pereyra M, Ali NB, et al. Left Atrial Strain: State of the Art and Clinical Implications. *J Pers Med*. 2024 Nov 5;14(11):1093. doi:10.3390/jpm14111093 PubMed PMID: 39590585.
3. Zhu H, Yang C, Li Y, Guo Y, Meng X, Ren Y, et al. Two-Dimensional Speckle Tracking Echocardiography Identifies Coronary Artery Disease in 690 Patients: A Retrospective Study from a Single Center. *Med Sci Monit Int Med J Exp Clin Res*. 2021 Feb 9;27:e929476-1-e929476-9. doi:10.12659/MSM.929476 PubMed PMID: 33561114; PubMed Central PMCID: PMC7883402.
4. Atici A, Barman HA, Durmaz E, Demir K, Cakmak R, Tugrul S, et al. Predictive value of global and territorial longitudinal strain imaging in detecting significant coronary artery disease in patients with

- myocardial infarction without persistent ST-segment elevation. *Echocardiography*. 2019 Mar;36(3):512–20. doi:10.1111/echo.14275 PubMed PMID: 30803009.
5. Ferkh A, Clark A, Thomas L. Left atrial phasic function: physiology, clinical assessment and prognostic value. *Heart*. 2023 Oct 26;109(22):1661–9. doi:10.1136/heartjnl-2022-321609 PubMed PMID: 36918267.
6. O'Neill T, Kang P, Hagendorff A, Tayal B. The Clinical Applications of Left Atrial Strain: A Comprehensive Review. *Medicina (Mex)*. 2024 Apr 24;60(5):693. doi:10.3390/medicina60050693 PubMed PMID: 38792875; PubMed Central PMCID: PMC11123486.
7. Cau R, Bassareo P, Suri JS, Pontone G, Saba L. The emerging role of atrial strain assessed by cardiac MRI in different cardiovascular settings: an up-to-date review. *Eur Radiol*. 2022 Jul;32(7):4384–94. doi:10.1007/s00330-022-08598-6 PubMed PMID: 35451607; PubMed Central PMCID: PMC9213357.
8. El Khoudary SR, Aggarwal B, Beckie TM, Hodis HN, Johnson AE, Langer RD, et al. Menopause Transition and Cardiovascular Disease Risk: Implications for Timing of Early Prevention: A Scientific Statement From the American Heart Association. *Circulation*. 2020 Dec 22;142(25):e506–32. doi:10.1161/CIR.0000000000000912 PubMed PMID: 33251828.
9. Pezel T, Michos ED, Varadarajan V, Shabani M, Venkatesh BA, Vaidya D, et al. Prognostic value of a left atrioventricular coupling index in pre- and post-menopausal women from the Multi-Ethnic Study of Atherosclerosis. *Front Cardiovasc Med*. 2022 Nov 21;9:1066849. doi:10.3389/fcvm.2022.1066849 PubMed PMID: 36479563; PubMed Central PMCID: PMC9719991.
10. Honigberg MC, Pirruccello JP, Aragam K, Sarma AA, Scott NS, Wood MJ, et al. Menopausal age and left ventricular remodeling by cardiac magnetic resonance imaging among 14,550 women. *Am Heart J*. 2020 Nov;229:138–43. doi:10.1016/j.ahj.2020.08.005 PubMed PMID: 32827459; PubMed Central PMCID: PMC7669696.
11. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, et al. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. *N Engl J Med*. 2019 Oct 24;381(17):1609–20. doi:10.1056/NEJMoa1908655 PubMed PMID: 31475794.
12. Subramanya V, Zhao D, Ouyang P, Ying W, Vaidya D, Ndumele CE, et al. Association of endogenous sex hormone levels with coronary artery calcium progression among post-menopausal women in the Multi-Ethnic Study of Atherosclerosis (MESA). *J Cardiovasc Comput Tomogr*. 2019;13(1):41–7. doi:10.1016/j.jcct.2018.09.010 PubMed PMID: 30297127; PubMed Central PMCID: PMC6359942.
13. Santema BT, Ouwerkerk W, Tromp J, Sama IE, Ravera A, Regitz-Zagrosek V, et al. Identifying optimal doses of heart failure medications in men compared with women: a prospective, observational, cohort study. *Lancet*. 2019 Oct 5;394(10205):1254–63. doi:10.1016/S0140-6736(19)31792-1 PubMed PMID: 31447116.
14. Zhao D, Guallar E, Ballantyne CM, Post WS, Ouyang P, Vaidya D, et al. Sex Hormones and Incident Heart Failure in Men and Postmenopausal Women: The Atherosclerosis Risk in Communities Study. *J Clin Endocrinol Metab*. 2020 Oct 1;105(10):e3798–3807. doi:10.1210/clinem/dgaa500 PubMed PMID: 32770207; PubMed Central PMCID: PMC7455306.
15. Sung KT, Chandramouli C, Lo CI, Tsai JP, Lai YH, Hsiao CC, et al. Association of Female Menopause With Atrioventricular Mechanics and Outcomes. *Front Cardiovasc Med*. 2022 Apr 21;9:804336. doi:10.3389/fcvm.2022.804336 PubMed PMID: 35528841; PubMed Central PMCID: PMC9068967.
16. Kolesnyk MY, Sokolova MV. Reliability of two-dimensional speckle tracking echocardiography in assessment of left atrial function in postmenopausal hypertensive women. *Zaporozhye Med J*. 2018;20(1):19–25.
17. Badano LP, Koliass TJ, Muraru D, et al. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force. *Eur Heart J Cardiovasc Imaging*. 2018;19(6):591–600.
18. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28(1):1–39.e14.
19. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29(4):277–314.

20. Ma CS, et al. The novel left atrial strain parameters in diagnosing of heart failure with preserved ejection fraction. *Echocardiography*. 2022;39(3).
21. Zhao Z, Wang H, Jessup JA, et al. Role of estrogen in diastolic dysfunction. *Am J Physiol Heart Circ Physiol*. 2014;306(5):H628-H640.
22. Mahmoodzadeh S, Dworatzek E. The role of 17 β -estradiol and estrogen receptors in regulation of Ca²⁺ channels and mitochondrial function in cardiomyocytes. *Front Endocrinol*. 2019;10:290.
23. Ventura-Clapier R, Piquereau J, Veksler V, Garnier A. Estrogens, estrogen receptors and heart failure. *Arch Cardiovasc Dis*. 2017;110(1):58-67.
24. Yuda S, Muranaka A, Miura T. Clinical implications of left atrial function assessed by speckle tracking echocardiography. *J Echocardiogr*. 2016;14:104-112.
25. Chamberlain R, Edwards NF, Scalia GM, Chan J. Novel left and right ventricular strain analysis to detect subclinical myocardial dysfunction in cardiac allograft rejection. *Int J Cardiovasc Imaging*. 2022;38(5):1077-1088.
26. Cameli M, Caputo M, Mondillo S, Ballo P, Palmerini E, Lisi M, et al. Feasibility and reference values of left atrial longitudinal strain imaging by two-dimensional speckle tracking. *Cardiovasc Ultrasound*. 2009;7:6. doi:10.1186/1476-7120-7-6.
27. Mirea O, Duchenne J, Voigt JU. Comparison between nondedicated and novel dedicated tracking tool for right ventricular and left atrial strain. *J Am Soc Echocardiogr*. 2022;35(4):419-425.
28. Silva MR, Sampaio F, Braga J, Ribeiro J, Fontes-Carvalho R. Left atrial strain evaluation to assess left ventricle diastolic dysfunction and heart failure with preserved ejection fraction: a guide to clinical practice. *Int J Cardiovasc Imaging*. 2023:1-14.
29. van Mourik MJ, Linz D, Verwijs HJ, Bekkers SC, Weerts J, Schotten U, et al. Evaluating subclinical left ventricular and left atrial dysfunction in idiopathic atrial fibrillation: a speckle-tracking based strain analysis. *Int J Cardiol*. 2023;383:159-165.
30. Ferkh A, Clark A, Thomas L. Left atrial phasic function: physiology, clinical assessment and prognostic value. *Heart*. 2023.
31. Deferm S, Martens P, Verbrugge FH, Bertrand PB, Dauw J, Verhaert D, et al. LA mechanics in decompensated heart failure: insights from strain echocardiography with invasive hemodynamics. *JACC Cardiovasc Imaging*. 2020;13(5):1107-1115.
32. Mauermann E, Bouchez S, Bove T, Vandenheuvel M, Wouters P. Assessing left ventricular early diastolic velocities with tissue Doppler and speckle tracking by transesophageal and transthoracic echocardiography. *Anesth Analg*. 2021;132(5):1400-1409.
33. Kreimer F, Gotzmann M. Left atrial cardiomyopathy: a challenging diagnosis. *Front Cardiovasc Med*. 2022;9:942385.
34. Nielsen AB, Skaarup KG, Lassen MCH, Djernaes K, Hansen ML, Svendsen JH, et al. Usefulness of left atrial speckle tracking echocardiography in predicting recurrence of atrial fibrillation after radiofrequency ablation: a systematic review and meta-analysis. *Int J Cardiovasc Imaging*. 2020;36:1293-1309.