STATE-OF-THE-ART REVIEW

Evaluation of Left Atrial Size and Function: Relevance for Clinical Practice

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Left atrial (LA) structural and functional evaluation have recently emerged as powerful biomarkers for adverse events in a variety of cardiovascular conditions. Moreover, noninvasive evaluation of LA pressure has gained importance in the characterization of the hemodynamic profile of patients. This review describes the methodology, benefits and pitfalls of measuring LA size and function by echocardiography and provides a brief overview of the prognostic utility of newer echocardiographic metrics of LA geometry and function (i.e., three-dimensional volumes, longitudinal strain, and phasic function parameters). (J Am Soc Echocardiogr 2020;33:934-52.)

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Left atrial (LA) enlargement and/or dysfunction are increasingly recognized as biomarkers for adverse cardiovascular events. Previously, only LA maximal size was considered to be a clinically relevant prognostic marker.[1] Recently, both minimal LA volume (LAV_{min})[2] and phasic function parameters[3,4] have been reported to be powerful predictors of outcome in various cardiac conditions. Moreover, noninvasive estimation of LA pressure has gained importance to fully characterize the hemodynamic profile of patients.[5]

However, despite the mounting evidence on the diagnostic and prognostic utility of these new echocardiographic metrics used to describe LA size and function, only LA maximal volume (LAV_{max}) is routinely reported in clinically indicated echocardiography studies.[6,7] Therefore, to encourage the wider uptake of the use of these new parameters of LA size and function, we provide a comprehensive overview of the evaluation of LA size and function, and pressure estimation using contemporary echocardiography (Figure 1) and a summary of their demonstrated diagnostic and prognostic value.

LA SIZE

Left atrial volume is a surrogate marker of the severity and chronicity of left ventricular (LV) diastolic dysfunction.[5] Additionally, LAV_{max} is a biomarker for adverse cardiac events both in healthy individuals and in various cardiovascular conditions[8,9] including myocardial infarction,[10] heart failure (HF),[11] stroke,[12] degenerative mitral regurgitation,[13] and atrial fibrillation (AF).[14]

Two-dimensional (2DE) and, recently, three-dimensional (3DE) echocardiography are the most commonly employed noninvasive imaging techniques to evaluate LA size.[3,5] Historically, the anterior-posterior LA diameter obtained either from M-mode or two-dimensional (2D) images from the parasternal long-axis view was utilized. However, LA diameter underestimates LA size[15,16] as LA enlargement is asymmetrical. Using LA diameter identified only 49% of patients with an enlarged LA, versus 76% identified by evaluating LA volume.[16,17]

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Abbreviations

2D = Two-dimensional

3D = Three-dimensional

2DE = Two-dimensional echocardiography

3DE = Three-dimensional echocardiography

AF = Atrial fibrillation

ASE = American Society of Echocardiography

CMR = Cardiac magnetic resonance

CT = Computed tomography

DOR = Diagnostic odds ratio

EACVI = European Association of Cardiovascular Imaging

ECG = Electrocardiogram

EmF = Emptying fraction

HF = Heart failure

HFpEF = Heart failure with preserved ejection fraction

LA = Left atrium/atrial

LAVI = Left atrial maximum volume index

LAV_{max} = Maximal left atrial volume

LAV_{min} = Minimal left atrial volume

LAV_{preA} = Left atrial volume before the P wave on electrocardiogram

LV = Left ventricle/ventricular

PALS = Peak atrial longitudinal strain

PCWP = Pulmonary capillary wedge pressure

STE = Speckle-tracking echocardiography

TDI = Tissue Doppler imaging

VTI = Velocity-time integral

Biplane LA volume is currently recommended to evaluate LA size[6] and is a stronger predictor of outcomes than linear dimensions.[1,18] However, measurement of 2DE LA volume requires acquisitions of dedicated apical views optimized for the LA.[6] The long axis of the LV is not parallel to the long axis of the LA[6,19] (Figure 2). Accordingly, measurements should be obtained from apical views that maximize the LA base and its maximum length, ensuring similar length of the LA in both apical views. When tracing the endocardial border, the LA appendage, the pulmonary veins, and the funnel of the mitral valve leaflets should be excluded (Figure 1). Phasic LA volumes are calculated by measuring LA volumes at various times of the cardiac cycle: LAV_{max} is measured just before mitral valve opening, pre-A LA volume (LAV_{PreA}) at the onset of the P wave on the electrocardiogram (ECG), and LAV_{min} at end diastole (before mitral valve closure). Parameters of phasic LA function (active and passive emptying volume and fraction and conduit volume) are calculated from these volumes (Table 1).[20]

Biplane 2DE LA volume can be measured using two algorithms: the modified Simpson's method of disk summation and the area-length method.[6] Both methods correlated with measurements obtained using computed tomography (CT).[21] The biplane area-length method systematically yields larger LA volumes than the disk summation method.[22,23] However, both methods have comparable prognostic power.[23] More recently, a novel 2DE tissue tracking technique to trace the endocardium can provide volumes that correlate well with 3DE LA volumes, while demonstrating less interobserver variability than manual tracing.[24]

Body size is a determinant of LA size, and absolute LA volumes are larger in men than in women[20]; indexation to body surface area (LAVI) corrects for the effect of sex[6,22] Two-dimensional echocardiography LA volumes have been similar in population-based studies[18] and in studies of healthy volunteers.[25] The effects of healthy aging on LA volume have been controversial, with some studies reporting an increase in LA volumes only at extremes of age,[25] while others demonstrate a progressive age-related increase in LA volume.[26] Differences in LA size (both LA diameter and volume) according to ethnicity suggested larger LA size for Europeans compared to South and East Asians; these differences persisted after indexation to body surface area and height.[27]

The threshold value for LA enlargement by 2DE was revised in the 2015 European Association of Cardiovascular Imaging (EACVI)/ American Society of Echocardiography (ASE) guidelines for chamber quantification.[6] The previous upper threshold value of the LAV_{max} has been raised from 28 to 34 mL/m^2, based on pooled data from larger cohorts of healthy subjects,[6] and aligns with the cutoff value used to define LA dilatation in the LV diastolic function algorithm.[28] Moreover, the revised value of >34 mL/m^2 to define LA enlargement is perhaps more clinically relevant, as an LAV_{max} >32 mL/m^2 was associated with adverse outcomes in ischemic stroke, diabetes, and HF.[1,29-31] Finally, the revised threshold for an enlarged LA allowed the reclassification into normal LA size for 21% of patients previously reported as having an enlarged LA, without any loss of the prognostic power associated with an enlarged LA.[23]

The problem with currently recommended partition values (mild LA enlargement LAV_{max} = 35-41 mL/m^2, moderate LA enlargement LAV_{max} = 42-48 mL/m^2, and severe LA enlargement LAV_{max} > 48 mL/m^2) is the narrow range of the varying grades. Thus, even small measurement errors can result in misclassification of the grade of LA enlargement. The recent multicenter Normal Reference Ranges for Echocardiography study, which included 734 healthy individuals, suggested that the normal limits for LAV_{max} may be even larger than the current 34 mL/m^2 threshold (up to 42 mL/m^2 using the area-length and 37 mL/m^2 using the Simpson's method).[22]

Two-dimensional echocardiography LA volume correlates with LA volumes obtained using 3DE,[32] CT,[33] and cardiac magnetic resonance (CMR),[34] with 2DE demonstrating a systematic underestimation of LA volumes.[35-37] This is likely due to the foreshortening of the LA in the absence of dedicated acquisitions to maximize the LA long axis. Moreover, difficult endocardial border definition, particularly in the two-chamber view,[32] may reduce the accuracy of measurements.[37] Notwithstanding these limitations, the ease of use and wide availability of 2DE makes it a clinically powerful tool, and it boasts the largest body of evidence on the alterations in LA volumes, as well as on its prognostic value (discussed in detail later).

In the last decade, 3DE has become the modality of choice to measure cardiac chamber volumes, with lower interobserver variability and higher test-retest reproducibility compared with 2DE, making it the preferred echocardiographic technique for serial measurements.[38] Using the most recent systems, 3DE LA data sets have acceptable frame rates using single-beat acquisition. Both semiautomated and fully automated contour detection algorithms have good correlations with manual tracing, with significant reduction in analysis times and improved reproducibility.[39,40] In a multicenter study of 92 patients with varying LAV, the agreement for classification for "an enlarged" LA using a cutoff of 34 mL/m^2 had a kappa coefficient of inter-rater agreement of 0.88 (four false negatives and seven false positives) between 3DE LA volume and CMR, compared with a kappa of 0.71 (25 false negatives and two false positives) for 2DE.[35] While Simpson's method of disks was previously applied,[41] more recently, fully automated 3DE wall motion tracking and pattern recognition methods, which identify natural ultrasonic speckles to evaluate myocardial motion, have been developed.[42,43] However, these newer algorithms (Figure 3) require further clinical validation.

HIGHLIGHTS

- The LA is emerging as a biomarker for evaluation of diastolic dysfunction, AF, and HFpEF.
- LA size, although routinely evaluated by 2DE, may be more accurately evaluated by 3DE.
- LA function is important and may demonstrate alterations prior to changes in LA volume.
- Both volumetric and strain analysis can be performed to evaluate LA phasic function.
- Noninvasive evaluation of LA pressure is emerging as an important modality.

Three-dimensional echocardiography LA volumes correlate better than 2DE with both CT[41] or CMR volumes.[34,35] Two studies sought to define reference values of three-dimensional (3D) LA volumes by adapting 3DE software algorithms developed for the LV to measure the LA.[40,44] A recent study of 276 of healthy subjects utilized a 3D software package specific for the LA, showing that 3DE LA phasic volumes were significantly larger than those obtained by 2DE[19] (Table 1). Similar to 2DE LA volume, indexation to body surface area of 3DE LA volumes eliminated sex differences, and a small yet significant increase in 3DE LA volume was observed with aging.

Fully automated 3DE LA volumes can be obtained using dedicated software packages available on recent high-end ultrasound systems (Figure 3). Moreover, the availability of single-beat acquisitions allows reliable LA 3DE quantification even in patients with AF. The major limitations at present are the limited spatial resolution of 3DE data sets and the paucity of data for both normative values, as well as prognostic value of 3DE LA volumes and phasic function indices.

Take-Home Messages

Linear Dimensions. Not to be used anymore since they are not related to actual LA size, particularly if the LA is enlarged.

2DE LA Volumes. Strengths: Easy to perform, widely available, do not require propriety software, with a large body of both normative data and data demonstrating prognostic value in various cardiac conditions.

Weaknesses: Underestimate the actual LA volume, needs dedicated LA views, depends on geometric assumptions for volume calculations, and interobserver variability and repeatability are less optimal.

3DE LA Volumes. Strengths: No geometric assumptions and therefore more accurate volumes, less interobservor variability, ideal for serial measurements.

Weaknesses: Poor spatial resolution, require specific transducer for image acquisition and particular software for measurements, increased cost, and paucity of supporting normative and prognostic data.

LA FUNCTION

Left atrial function plays a key role in maintaining optimal cardiac performance. The LA modulates LV filling by acting as (1) a reservoir (during LV systole and isovolumic relaxation) receiving blood from the pulmonary veins and storing energy in the form of pressure; (2) a conduit (during early LV diastole and diastasis), transferring blood passively from the pulmonary veins into the LV by a small pressure gradient; (3) a contractile pump (during late LV diastole), augmenting LV stroke volume by 20%-30% in normal subjects and relatively more in the presence of LV systolic dysfunction; (4) a suction source that refills itself in early systole.[45,46] The main determinants of LA phasic function illustrate the interplay that exists between LA and LV performance. Left atrial reservoir function is modulated by both LV contraction (mediated through the descent of the LV base during systole) and LA compliance (relaxation and chamber stiffness).[47] The LA conduit function, in early diastole, is predominantly modulated by LV relaxation and compliance and early diastolic pressures, with a limited contribution from LA compliance. The LA booster pump function is modulated predominantly by LV end-diastolic pressure and LA intrinsic contractility, with a limited contribution from LV compliance.[48]

Volumetric Parameters of LA Function

The volumetric method used to assess LA function is based on LA volumes measured at the end of LV systole (LAV_{max}), before the onset of the P wave on the ECG tracing (LAV_{preA}) and at the end of LV diastole (LAV_{min}, see above), calculating the following indices[49]:

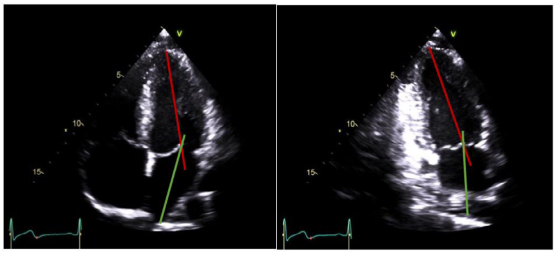
LA total emptying fraction (EmF) = $(LAV_{max} - LAV_{min})/LAV_{max} \times 100$ (for LA reservoir function),
LA expansion index = $(LAV_{max} - LAV_{min})/LAV_{min} \times 100$ (for LA reservoir function),
LA passive EmF = $(LAV_{max} - LAV_{PreA})/LAV_{max} \times 100$ (for LA conduit function),
LA active EmF = $(LAV_{PreA} - LAV_{min})/LAV_{PreA} \times 100$ (for LA contractile function).

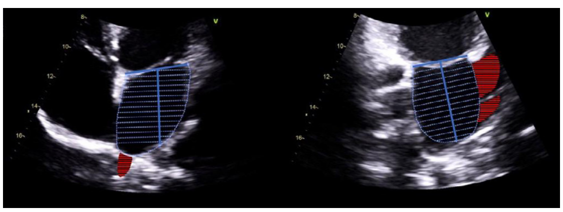
These parameters can be assessed by different imaging techniques: 2DE and 3DE,[19,50,51] cardiac CT,[52] or CMR.[53] Measurement of LA phasic volumes using 2DE is time-consuming and prone to error because of the need of three manual endocardial tracings of LA volumes based on the different timing of the various atrial events and the geometric assumptions of the biplane algorithms about the shape of the LA. Using 3DE data sets and dedicated software packages for LA volume quantitation, the assessment of LA phasic volumes and function parameters have become accurate and reproducible (different from the ventricles, LA walls do not have trabeculations) and less time-consuming (the endocardial surface is automatically mapped by the algorithm; Figure 3). Reference values of LA phasic function, measured by 3DE have been reported.[19,51] Left atrial total emptying and passive EmF measured by 3DE are larger than their corresponding measurements by 2DE.[19] Conversely, the LA expansion index and LA active EmF were similar, measured by either 3DE or 2DE.[19] The effect of age on LA phasic functions remains controversial. Regardless of whether 3DE[19] or 2DE[20] is used for the assessment of LA function, age-related decrease of the LA passive EmF seems to be counterbalanced by an increase of the active EmF. The 3D-derived LA expansion index also decreases with age.[19] The load dependence of LA volumetric indices represents the main limitation for the assessment of LA function with this method, regardless of the imaging technique used.

Take-Home Messages

2DE Volumetric Phasic LA Volumes. Strengths: Do not require propriety software, modest body of supporting data.

Biplane LA volumes

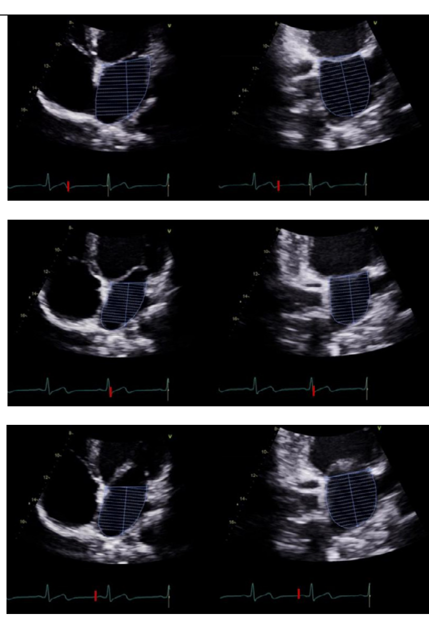




Technique

- Optimize the left atrium (LA) by acquiring dedicated, non foreshortened apical 4- and 2-chamber views in which LA cavity is maximized both longitudinally and transversally (i.e. different plane orientation from the conventional apical views optimized for the left ventricle (LV)
- Zoom on LA, including the mitral annulus and superior LA wall (roof)
- Trace the blood-tissue interface in both views at end-systole (just prior to mitral valve opening)
- Adjust LA length in a direction perpendicular from the mid point of mitral annular plane to the mid point of LA superior wall
- If properly acquired, LA length should not vary by more than 5 mm between 4-chamber and 2-chamber views
- When tracing the LA wall, do not include the space between the annulus and the mitral valve leaflets, left atrial appendage or pulmonary veins
- Biplane disc summation method is recommended for LA volume calculation, as it includes fewer geometric assumptions than the area-length method which assumes an elliptical LA.
- LA volumes should be indexed to body surface area

Phasic LA volumes and function



Technique

Measurement of LA volumes at three different frames of the cardiac cycle:

1. LA maximum volume (LAV_{max}):
   LA volume at LV end-systole (just before mitral valve opening) (mL/m^2)
2. LA minimum volume (LAV_{min}):
   LA volume at end-diastole (at mitral valve closure) (mL/m^2)
3. Pre A volume (LAV_{preA}):
   LA volume at the onset of P wave on the ECG (mL/m^2)

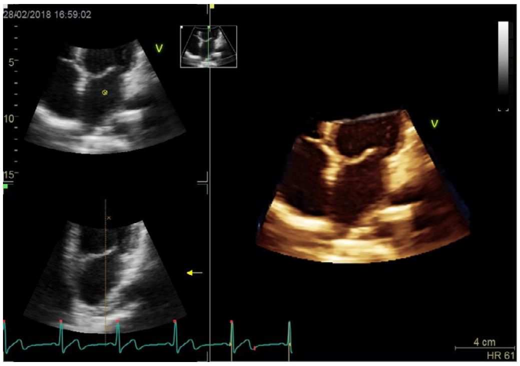
Calculation

LA Reservoir Function
- LA total emptying volume = LAV_{max}- LAV_{min} (mL/m^2)
- LA expansion index = LA total emptying volume/LAV_{min} (%)

LA Conduit Function
- LA passive emptying volume = LAV_{max} - LAV_{preA} (mL/m^2)
- LA passive emptying fraction = LA passive emptying volume / LAV_{max} (%)
- LA conduit volume = LV stroke volume -LA total emptying volume (mL/m^2)

LA Active Contractile Function
- LA active emptying volume = LAV_{preA} - LAV_{min} (mL/m^2)
- LA active emptying fraction = LA active emptying volume / LA_{preA} (%)

Figure 1 Overview of the various parameters employed to assess LA size and function using contemporary echocardiography.

3D LA volumes	Technique
	● Optimize LA image quality - adjust probe position for a complete visualization of LA contour in all views throughout the cardiac cycleoptimize gain settings for high signal-to noise ratio of LA walls - avoid artifacts ● Optimize temporal resolution - reduce the volume size to the minimum necessary to include the LA cavity - exclude the right atrium and right ventricle - adjust the depth for including only the LA roof, and eliminate deeper extracardiac structures from the acquisition - whenever feasible, obtain a multi-beat acquisition to maximize frame-rate (particularly recommended for the assessment of LA phasic function)

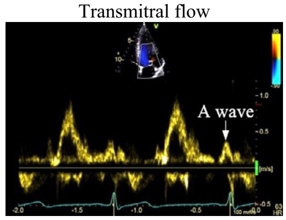
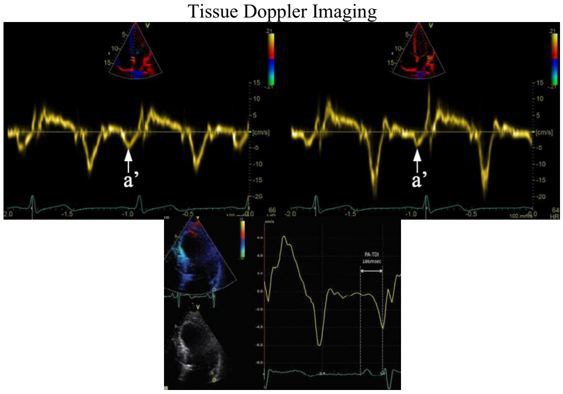
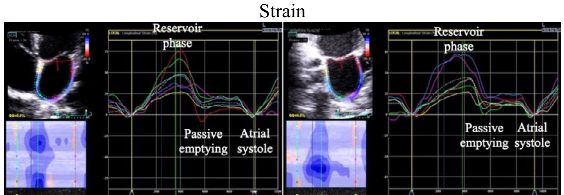
LA function	Technique
Transmitral flow  	● Transmitral flow: Place sample volume at mitral valve leaflet tips, acquire at sweep speed of 100mm/s Peak A wave velocity, A wave velocity time integral, A wave duration, Atrial fraction (A wave VTI/ total VTI x100) Atrial ejection force= 0.5 x 1.06 x mitral orifice area x (A vel)^2
Tissue Doppler Imaging  	● Tissue Doppler Imaging: Late diastolic a' wave peak velocity from both septal and lateral mitral annulus Atrial conduction time (PA TDI) measured as duration from onset of ECG p wave to peak a' velocity using pulsed wave or colour TDI (see fig)
Strain  	● Longitudinal Strain: Obtain unzoomed LA focused and optimized view Acquire 3-5 cardiac cycles at high frame rates (>55fps) Optimize 2D image quality LA reservoir phase: peak positive longitudinal strain in systole LA passive emptying = longitudinal strain in early diastole LA active contraction = longitudinal strain in late diastole

Figure 1 (Continued).

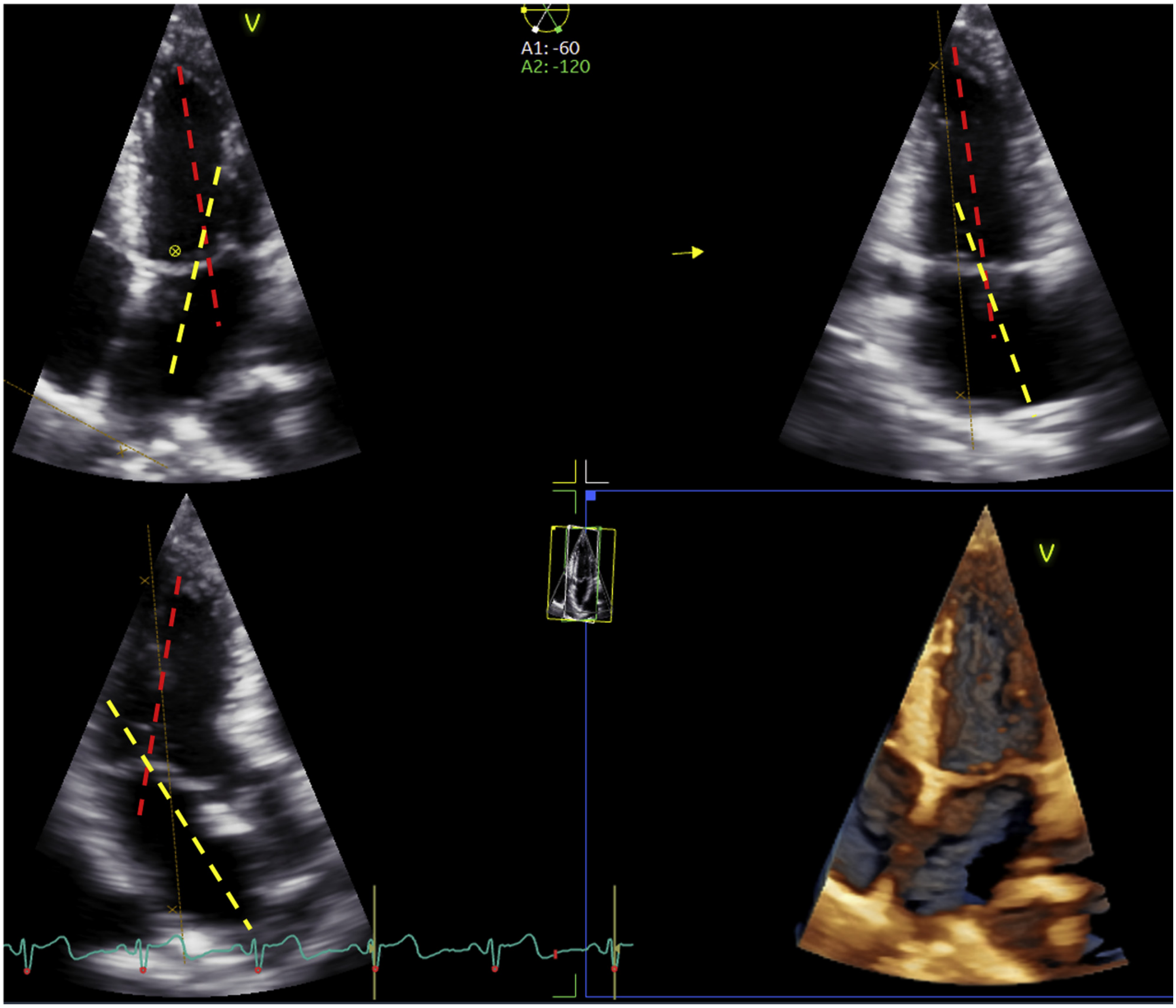


Figure 2 Three-dimensional anatomic heart model and 3DE rendering, illustrating the fact that the long axis of the LV and LA do not lie in the same plane.

Weaknesses: Three separate manual tracings are required thereby increasing errors, need focused LA views, geometric assumptions for volume estimation, large interobservor and test/retest variability.

3DE Volumetric Phasic LA Volumes. Strengths: Fully or semiautomated endocardial border tracings, small-modest body of supporting data.

Weaknesses: Require proprietary software packages, increased costs, and others as mentioned in 3DE LA volumes.

DOPPLER PARAMETERS OF LA FUNCTION

The assessment of transmitral inflow pattern by pulsed-wave Doppler sampling at the level of mitral leaflet tips can provide a broad estimate of LA function. The transmitral A wave, a surrogate marker of LA contractile function, was commonly used to assess LA function during serial follow-up studies after cardioversion of AF to sinus rhythm[54] (Figure 4) or after catheter-based ablation techniques.[55] The velocity and duration of LV filling during active atrial contraction should in principle reflect the LA pump function. The higher the peak A wave velocity and A wave velocity-time integral (VTI) from mitral inflow, the better the LA booster pump function. However, the transmitral flow pattern is influenced by several other factors such as heart rate, age,[56] loading conditions,[57] and LV diastolic properties, and therefore its usefulness for quantifying intrinsic LA contractile function is limited. Moreover, the analysis of transmitral inflow pattern is limited to patients in sinus rhythm for the assessment of LA booster pump function and is unable to provide information about the reservoir and conduit phases of LA function.

Calculated as the ratio between VTI of the A wave and VTI of the whole diastolic transmitral flow, the atrial fraction may also be used as an estimate of LA contractile function[58]:

$$\text{Atrial fraction} = \text{VTI}_{\text{A wave}}/\text{VTI}_{\text{mitral inflow}}.$$

The atrial fraction demonstrated similar changes but with a slower normalization compared with peak A wave velocity with the restoration and maintenance of sinus rhythm after cardioversion of AF patients to sinus rhythm.[58]

Table 1 Reference values for 2D and 3D echocardiographic measurements of the LA[19]

Left atrial parameter	LA size				
	3DE	2DE	*P* value	Upper NL 3DE	Upper NL 2DE
Maximal volume, mL/m^2	32 ± 4	24 ± 6	<.001	<46	<34
Minimal volume, mL/m^2	11 ± 3	8 ± 3	<.001	<17	<14
PreA volume, mL/m^2	18 ± 5	15 ± 5	<.001	<28	<25
Total emptying volume, mL	38 ± 10	29 ± 7	<.001	—	—
Passive emptying volume, mL	25 ± 7	17 ± 6	<.001	—	—
Active emptying volume, mL	14 ± 6	12 ± 4	<.001	—	—

NL, normal limit.

The atrial ejection force represents the force exerted by the LA to propel blood across the mitral valve into the LV during atrial systole and can be estimated using the following equation[59]:

$$\text{Atrial ejection force} = 0.5 \times 1.06 \times \text{mitral annulus area} \times (\text{peak A velocity})^2.$$

This parameter has the same limitations as any parameter derived from transmitral flow. In addition, the calculation of the mitral annulus area by 2DE assumes that it is circle, with the diameter being measured in the apical four-chamber view. Moreover, its robustness, reproducibility, and incremental value over LA volumetric function have not been documented.[45]

All the above parameters of LA function derived from transmitral flow can be measured only in patients in sinus rhythm. In this context, the LA function index was used as a rhythm-independent parameter able to monitor LA function even in patients with AF.[60] Combining volumetric and Doppler-derived parameters, LA function index incorporates analogues of LA reservoir function, cardiac output, and LA size and is calculated as follows:

$$\text{LA function index} = \text{LA EmF} \times \text{VTI}_{\text{LVOT}}/\text{LAVI},\ \text{where LVOT is the LV outflow tract.}$$

The LA function index may be a more sensitive marker to identify deteriorating LA function over time due to AF or the persistent LA dysfunction after successful cardioversion.[60]

TISSUE DOPPLER IMAGING: A' VELOCITY AND PA-TDI

It has been demonstrated that peak velocity of the mitral annulus in late diastole (a') correlates with both LA EmF and LA ejection force and can be used as a marker of contractile LA function.[61] As late diastolic septal and lateral a' velocities are similar, either of the two sites can be sampled.[62] The a' velocity increases with age,[61] reflecting both the decrease in LV early diastolic compliance with aging and the increase in atrial booster pump contribution to LV filling.

Tissue Doppler imaging velocities can also be obtained from within LA segments; however, both annular and LA segmental tissue Doppler imaging (TDI) velocities cannot distinguish between active atrial contraction and passive LA wall translation and tethering from mitral annular displacement and ventricular contraction. Moreover, TDI is angle dependent, wall-by-wall sampling is time-consuming, and the different threshold values for normality for the different walls limit the use of this echocardiography technique in clinical practice. Finally, the LA wall is very thin, and it is very difficult to maintain the sample volume of the TDI within the thickness of the LA wall throughout the cardiac cycle.

The time to peak a' velocity from the onset of p wave on ECG (PA-TDI) has been used as a measure of total atrial conduction time and has been shown to be a predictor of new-onset AF[63] as well as AF recurrence postcardioversion.[64]

Take-Home Messages

Transmitral Flow. Strengths: Easy to perform on any ultrasound system, does not require proprietary software.

Weaknesses: Altered by loading conditions, age and heart rate, and mitral valve disease and can be used only in sinus rhythm; surrogate of LA contractile function.

LA Function Index. Strengths: Does not require propriety software, can be utilized in nonsinus rhythm, has functional and prognostic utility.

Weaknesses: Requires multiple parameters to be measured, relatively small number of published studies.

TDI Measurements: a' Velocity and PA-TDI. Strengths: Easy to perform, useful for timing measurement, modest body of supporting data, high temporal resolution for measurement of timing.

Weaknesses: Doppler-based technique reliant on angle of interrogation, utilized only in sinus rhythm, surrogate of LA contractile function.

STRAIN PARAMETERS OF LA FUNCTION

Strain and strain rate measure the magnitude and the rate of LA myocardial deformation.[65] Strain measurements allow discrimination between active myocardial deformation and passive wall motion, being relatively independent of the tethering effects[66] and less load dependent compared with volumetric parameters of LA function.[67] Left atrial strain by echocardiography is particularly relevant to evaluate the reservoir component of LA phasic function.[68-72] Left atrial strain measurements can be obtained by either TDI or 2D speckle-tracking echocardiography (STE).[73-75] Historically, TDI was the first ultrasound technique that offered insights into LA myocardial deformation. However, despite its high frame rate, the clinical applicability of TDI remains challenging due to its relatively low reproducibility and the dependence on the angle of insonation that

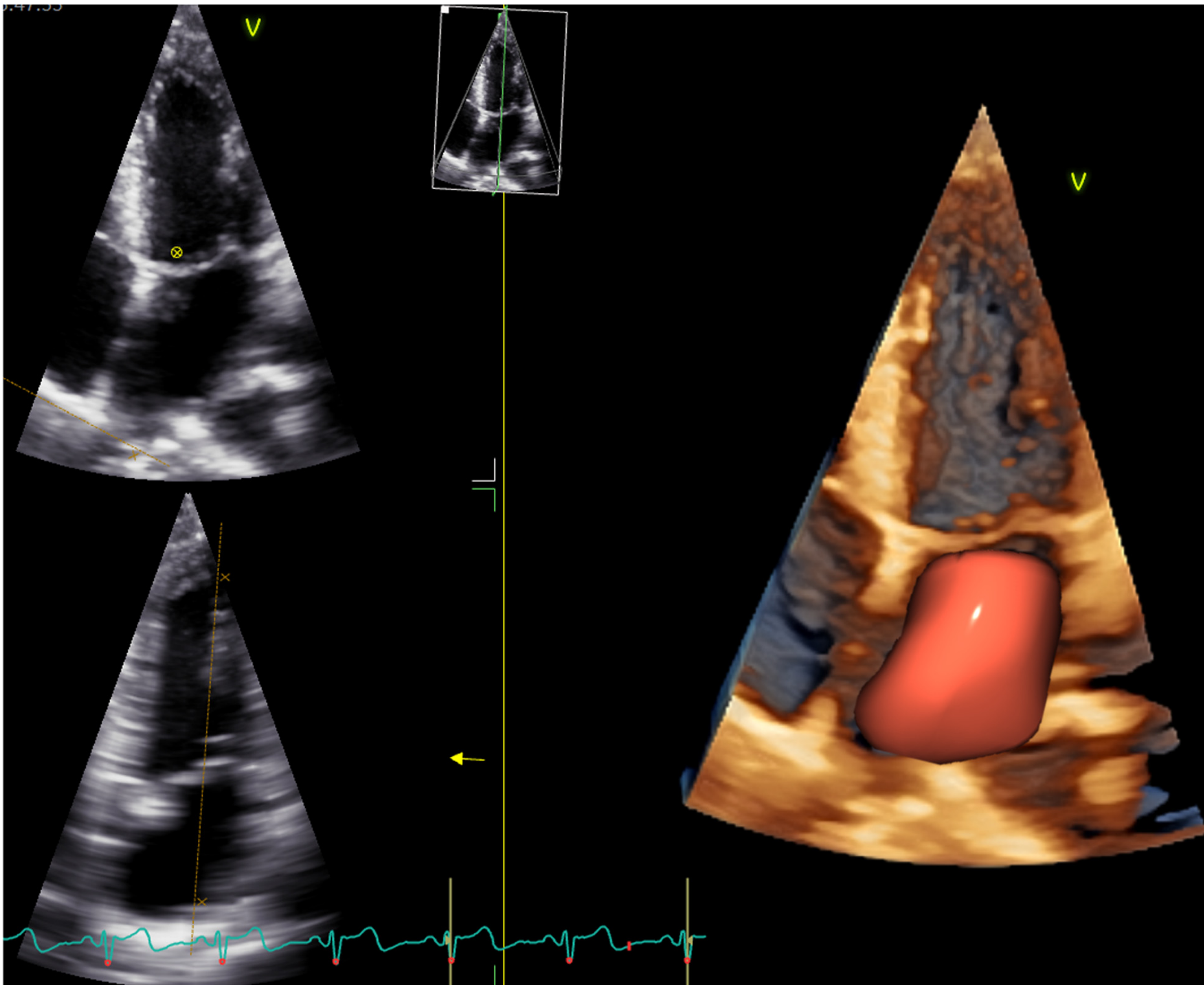


Figure 3 Automated measurements of the LA volumes using 3DE with commercially available software packages that use data sets acquired with the transthoracic approach.

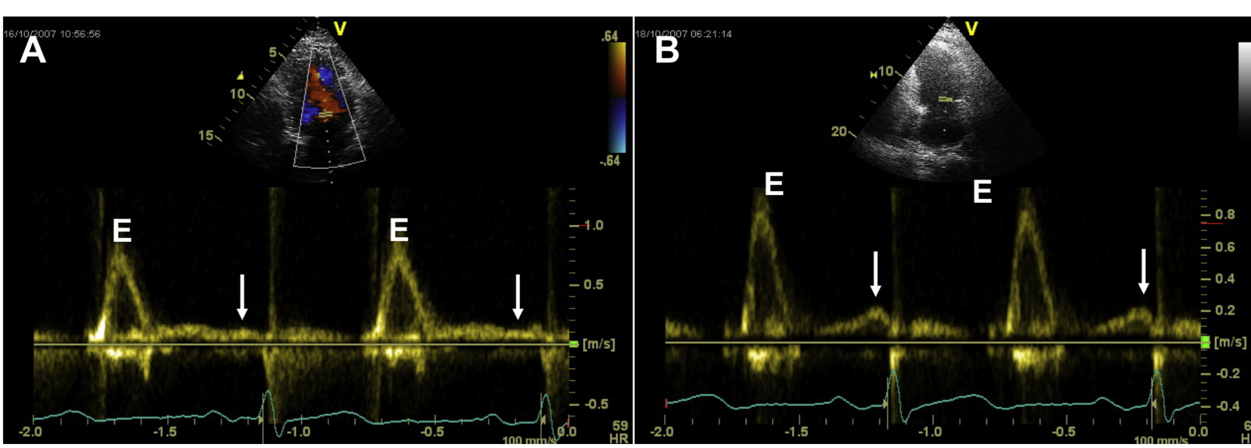


Figure 4 Delayed contractile atrial function recovery after restoring sinus rhythm by electric cardioversion of AF. **(A)** Transmitral flow immediately after successful cardioversion in sinus rhythm does not show any measurable A wave (*white arrows*). **(B)** Transmitral flow recorded in the same patients after 1 week, showing a low-velocity A wave (*white arrows*) documenting a restored mechanical activity of the LA.

limits the sampling only to limited segments of the LA that are aligned with the ultrasound beam.[76,77] Moreover, for accurate measurements, the sample volume needs to be manually tracked throughout the cardiac cycle, which is time-consuming.

Two-dimensional STE is currently the preferred technique for the routine measurement of LA strain, as it is semiautomated, less angle-dependent, and less affected by artifacts than TDI. Two-dimensional STE tracks frame by frame the natural acoustic markers ("speckles") within a region of interest (kernel) of the 2D ultrasound image and evaluates the geometric shift of each kernel throughout the cardiac cycle. A consensus document for standardization of LA strain analysis and nomenclature by STE from the EACVI/ASE/Industry Task Force initiative has been recently published.[65] For adequate tracking, a dedicated apical four-chamber view with relatively high frame rates (50-70 frames/sec) and optimization of the depth, gain, and orientation to obtain nonforeshortened views of LA walls throughout the cardiac cycle is recommended.[6,65] The region of interest is contoured, extrapolating across the pulmonary veins and LA appendage, and its thickness is reduced to fit the thin LA wall. The only recommended strain parameter of LA function is the global longitudinal strain.[65] In the reservoir phase, as the LA fills and stretches, there is positive longitudinal strain that reaches its peak in ventricular systole, at the end of LA filling, before the opening of the mitral valve. After mitral valve opening, passive LA emptying ensues, resulting in a decrease in LA strain up to a plateau period corresponding to diastasis. In sinus rhythm, a second smaller wave of the strain curve is observed after the plateau, corresponding to atrial systole (Figure 5).

Based on the reference timing of zero strain in the cardiac cycle, that is, at end diastole (R-R gating recommended by EACVI/ASE/Industry Taskforce[65]) or at the onset of atrial contraction (P-P gating[78]), the LA strain curve has two different patterns leading to different ways of obtaining LA phasic function parameters and variable strain measures (Figure 5). Strain rate during ventricular systole, early diastole, and late diastole corresponds to reservoir, conduit, and booster pump functions with both techniques.[79] The rationale in favor of using end diastole (R wave on ECG) as the zero reference point includes the fact that the R wave is easier than P wave to be automatically detected by software packages and because it can be used in patients with AF.[65] However, strain values obtained with any of the two techniques can be mathematically converted to the other one.[65]

The reference ranges of various strain parameters are crucial for the clinical implementation of LA strain assessment. Several studies have reported reference values for LA strain and strain rate in the past decade using TDI, 2D STE, or, recently, 3D STE techniques (Table 2). The differing sample size, age, and sex distribution of healthy subjects, as well as the lack of standardization of the methodology used for quantifying LA deformation in the past, have led to a significant heterogeneity in the reported normal values for LA strain parameters. Additionally, as no dedicated software package for LA strain quantification was available, different ultrasound systems and software packages dedicated to LV strain measurements have been adapted to measure LA strain.

Aiming to provide more robust reference ranges for LA strain parameters based on the available 2D STE studies, Pathan *et al.*[93] recently published a meta-analysis including 2,038 healthy subjects. The threshold values for normality were 39% for reservoir strain (95% CI, 38%-41%), 23% for conduit strain (95% CI, 21%-25%), and 18% for contractile strain (95% CI, 16%-19%). When implementing normative ranges of LA strain in clinical practice, it is important to take into account that these reference values are heavily weighted by 2D STE studies employing one vendor (85% of the studies used General Electric equipment), using end diastole as the zero reference point (R-R gating 93% of the studies).[93] After the publication of the common standards to assess LA strain,[65] manufacturers have started to develop dedicated software packages for LA strain measurements (Figure 6).

Using either 2D STE or TDI, it was demonstrated that LA strain parameters reflecting reservoir and conduit functions decrease with age.[51,78,94] In some studies, LA contractile strain had no significant relationship with age,[77,78,93] while in the multicenter Normal Reference Ranges for Echocardiography study, an increase with aging was reported.[51] One study showed that women have earlier and more pronounced age-related changes in LA reservoir and conduit strain than men.[78]

Most studies did not identify statistically significant differences of strain values between men and women in healthy

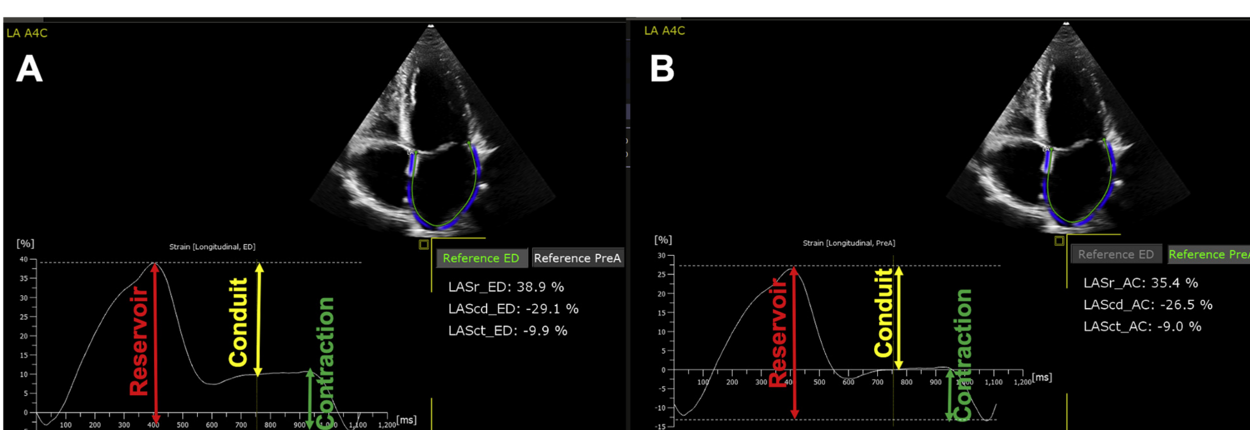


Figure 5 Dedicated software package to measure LA longitudinal strain using automated tracing of the LA endocardium in the apical four-chamber view and following the recommendations of the EACVI/ASE/Industry Task Force for strain standardization.[65] **(A)** Measurement of LA longitudinal strain using the R wave (end diastole, ED) as time reference. **(B)** Measurement of LA longitudinal strain using the P wave (atrial contraction, AC) as time reference. *LAScd*, LA longitudinal strain conduit; *LASct*, LA longitudinal strain contraction; *LASr*, LA longitudinal strain reservoir.

Table 2 Studies performed using 3D echocardiography and LA strain in patients with AF or risk of cardiac embolism

Reference	Methodology (population and technique)	Result
Identification of patients at risk of AF		
Hirose *et al.*[80]	Population: 580 patients without documented atrial arrhythmia. Atrial contractile strain: velocity vector imaging.	Subjects with new-onset AF had lower contractile function: Lower LA active EF (16% ± 5% vs 28% ± 8%, P = .001). Lower LA contraction strain rate (-0.9 ± 0.2 vs -1.4 ± 0.5 sec^{-1}, P < .001).
Summary: 580 patients with atrial arrhythmia, mainly AF; reduced LA contractile function (measured by volumetric LA active EmF and strain rate) was decreased in patients who developed AF.		
Pathan *et al.*[81]	Population: 538 Patients with cryptogenic stroke LA reservoir, conduit and contractile strain: 2D speckle-tracking	Patients who developed AF had lower atrial strain. Reservoir function: 21.3% ± 7.5% vs 32.7% ± 8.4%. Conduit function:11.7% ± 4.8% vs 17.4% ± 6.8%. Contractile function: 9.6% ± 4.2% vs 15.3% ± 4.4% (P < .001 in all).
Summary: 538 cryptogenic stroke patients evaluated with phasic LA function (reservoir, conduit and contractile), using strain. Stroke patients who developed AF had reduced phasic LA strain.		
Kosmala *et al.*[82]	Population: 146 patients with dual-chamber pacemaker for AF occurrence. LA reservoir conduit and contractile strain: 2D speckle-tracking.	Patients who developed AF had lower atrial strain. Reservoir function: 19.5% ± 9.2% vs 26.1% ± 9.6% (P = .002). Conduit function: 10.0% ± 5.2% vs 12.3% ± 6.2% (P = .04). Contractile function: 9.4% ± 5.5% vs. 13.8% ± 5.6% (P = .04).
Summary: 146 patients with pacemakers evaluated by phasic LA strain (reservoir, conduit and contractile) for subsequent development of AF. Phasic LA function was decreased in those with reduced LA phasic function.		
Schaaf *et al.*[83]	Population: 102 patients without heart disease versus 44 paroxysmal AF patients. Phasic LA function: 2D and 3D volumetric and speckle-tracking.	3DE: all phasic atrial functions were impaired in the paroxysmal AF group, regardless of the parameters used (all P = .05). 2DE: conduit function not significant.
Summary: 44 patients with paroxysmal AF compared to 102 patients without heart disease, with phasic LA function evaluated by 2D and 3D volumetric and strain measurement. Two-dimensional echocardiography demonstrated decrease in reservoir and contractile function. 3DE: all phasic atrial functions were impaired in the PAF group, regardless of the parameters used (all P = .05)		
Hubert *et al.*[84]	Population: 27 endurance athletes with paroxysmal AF vs 30 endurance athletes without AF. LA reservoir and conduit function: 2D volumetric and 2D speckle-tracking.	Atrial function decreased in the paroxysmal AF group. Reservoir function: LA ejection fraction: 59.3% ± 12.9% vs 67.6% ± 10.0% (P = .01); strain: 29.3% ± 7.9% vs 49.1% ± 7.8% (P < .0001). Conduit function: LA passive EmF: 36.0% ± 16.2% vs 37.9% ± 10.1% (P = .59); strain: 17.0% ± 6.2% vs 27.0% ± 6.7% (P < .0001). Contractile function: LA active EmF: 23.4% ± 9.6% vs 29.6% ± 9.0% (P = .014); strain: 12.3% ± 6.4% vs 22.0% ± 5.6% (P < .0001).
Summary: Endurance athletes with AF (n = 27) were compared to athletes without AF (n = 30), and LA reservoir, conduit, and contractile function were evaluated using 2D strain and phasic LA volumes. Phasic LA function was decreased in the subgroup with AF.		
Prediction of success of AF reduction		
Sarvari *et al.*[85]	Population: 61 patients with paroxysmal AF and 20 healthy controls. LA strain and mechanical dispersion: 2D speckle-tracking.	LA mechanical dispersion more pronounced with AF recurrence after radio frequency ablation vs those without and controls (38 ± 14 msec vs 30 ± 12 msec vs 16 ± 8 msec, both P = .001). LA strain reduced in both patients with and without recurrent AF after radio frequency ablation vs controls (−14% ± 4% vs −16% ± 3% vs −19% ± 2%, both P < .05).

(Continued)

Table 2 (Continued)

Reference	Methodology (population and technique)	Result
Summary: 61 paroxysmal AF patients were compared to 20 controls, and LA function was evalauated by LA strain and regional function by mechanical dispersion. Left atrial strain was reduced in patients with AF (including those with AF recurrence), compared to controls. Left atrial mechanical dispersion was greatest in those with AF recurrence but was also prolonged in those with paroxysmal AF.		
Montserrat *et al.*[86]	Population: 33 healthy volunteers and patients with symptomatic drug-refractory AF treated with RF ablation (n = 83) or a second RF ablation (n = 35). LA reservoir function: 2D speckle-tracking.	LA reservoir function was lower in second RFCA group versus first RFCA or controls, respectively (30% ± 5%, 20% ± 6%, 15% ± 5%, P < .05).
Summary: AF patients treated by RF ablation (n = 83) and repeat RF ablation (n = 35) and 33 controls were evaluated for LA function by 2D reservoir strain. Left atrial strain was lowest in those with a repeat RF ablation, intermediate in those with first RF ablation, and highest in controls.		
Montserrat *et al.*[87]	Population: 154 patients with AF treated with RF ablation. LA EmF and expansion index 3D volumetric measures on transesophageal echocardiography.	Patients with recurrent AF had lower atrial function. LA EmF: 32% ± 15% vs 40% ± 19% (P = .028). LA expansion index: 48.9% vs 78.9% (P = .016).
Summary: 154 AF patients treated with RF ablation were evaluated by LA EmF and LA expansion index. Patients with recurrent AF had reduced LA function.		
Prediction of reverse remodeling after RFCA		
Tops *et al.*[88]	Population: 148 AF patients treated by catheter ablation LA strain and LAVI: 2D volumetric LA reverse remodeling and TDI.	Baseline LA systolic strain higher in responders as compared to nonresponders (19% ± 8% vs 14% ± 6%; P = .001). LA reverse remodeling at follow-up: responders exhibited ≥15% reduction in LAVI at long-term follow-up.
Summary: 148 AF patients treated with catheter ablation, were evaluated by indexed LA volume and LA strain. LA strain was higher in patients in whom sinus rhythm was restored, with >15% reduction in indexed LA volume compared to baseline.		
Prediction of stroke		
Obokata *et al.*[89]	Population: patients with paroxysmal or persistent AF with acute embolism (82 patients) or without (204 controls). LA EmF and LA strain: volumetric and 2D speckle strain.	Atrial function was lower in patients with acute embolism. LA EmF: 20 ± 11 vs 28 ± 13, P < .001. Global LA strain: 12.6 ± 3.7 vs 18.9 ± 6.0, P < .001.
Summary: 82 patients with paroxysmal or persistent AF were compared to 204 controls, who were prospectively followed up for acute embolic events. In the 82 individuals who had an embolic event, volumetric LA EmF and LA reservoir strain were reduced.		
Azemi *et al.*[90]	Population: Patients with AF, stroke, or transient ischemic attack and $CHADS_2$ scores ≤1 before event compared versus controls. LA positive and negative strain: velocity vector imaging.	Atrial function reduced in patients versus controls. Peak negative LA strain (−3.2% ± 1.2% vs −6.9% ± 4.2%, P < .001). Peak positive LA strain (14% ± 11% vs 25% ± 12%, P < .001).
Summary: 57 patients with AF, stroke or transient ischemic attack with low $CHADS_2$ score (<1) evaluated by velocity vector imaging strain. Both reservoir (positive) and contractile strain (negative) were reduced in patients compared to controls.		
Leung *et al.*[91]	Population: 1,361 patients with first diagnosis of AF for stroke occurrence. LA reservoir and conduit strain: 2D speckle strain.	LA reservoir (14.5% vs 18.9%, P = .005) and conduit strain were reduced (10.5% vs 13.5%, P = .013) in the stroke group.
Summary: 1,361 patients evaluated after first presentation with AF, evaluated by LA reservoir and conduit function by 2D strain. Both reservoir and conduit strain were significantly reduced in those who subsequently developed a stroke compared to those who did not have a stroke.		
Prediction of stroke without documented AF		
Leong *et al.*[92]	Population: 742 cryptogenic stroke patients without AF history, 371 controls LA reservoir strain: 2D speckle strain.	LA reservoir strain was significantly lower among patients with cryptogenic stroke (30% ± 7.3% vs 34% ± 6.7%, P < .001).
Summary: 742 cryptogenic stroke patients compared to 371 controls by evaluated of LA reservoir strain, which was significantly reduced in the cryptogenic stroke group.		

RF, Radiofrequency; *RFCA*, radiofrequency catheter ablation.

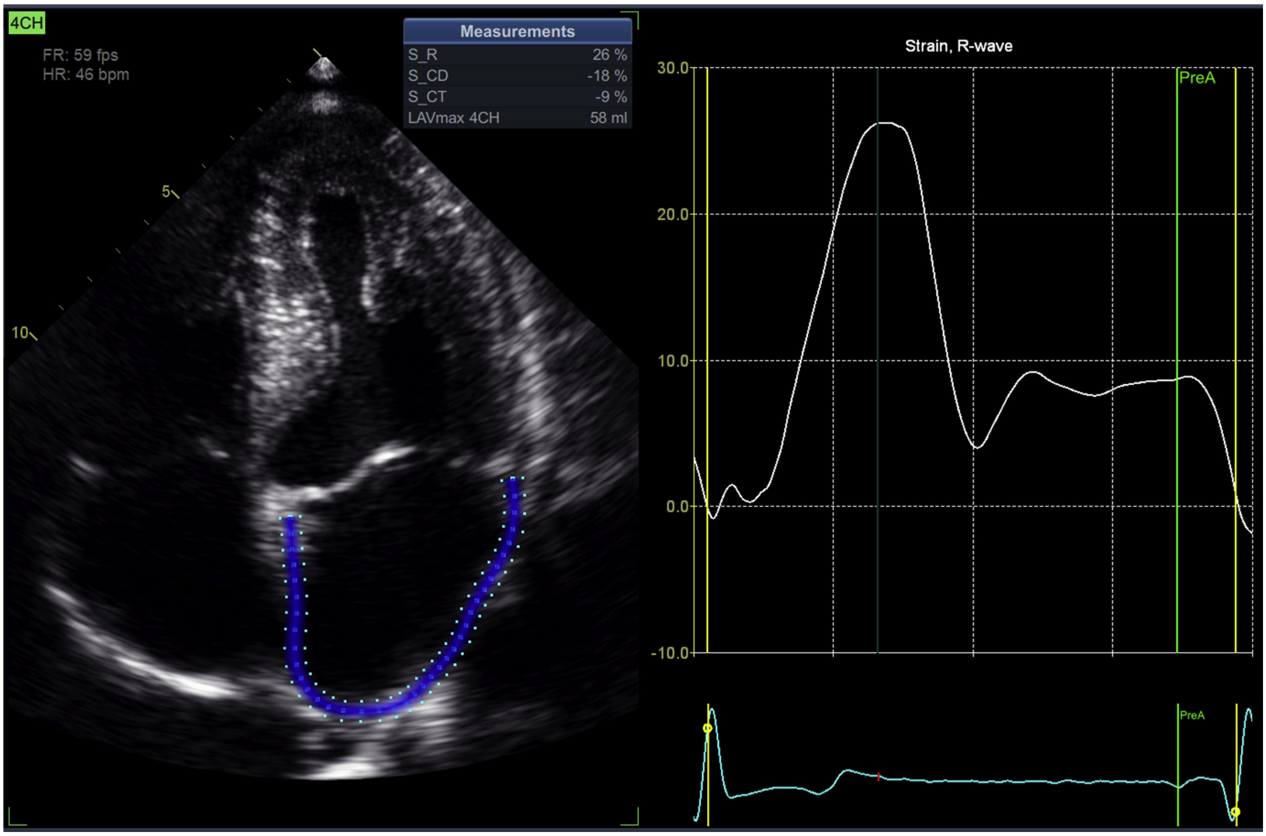


Figure 6 Dedicated software package to measure LA longitudinal strain using automated tracing of the LA endocardium in the apical four-chamber view and following the recommendations of the EACVI/ASE/Industry Task Force for strain standardization.[65] This software package measures LA longitudinal strain using the four-chamber apical view and R wave as the only time reference. In addition, the software package provides single-plane LA maximal volume (LAV_{max}). *S_CD*, LA longitudinal strain conduit; *S_CT*, LA longitudinal strain contraction; *S_R*, LA longitudinal strain reservoir.

individuals.[51,93-95] However, a study that stratified sexes according to age groups (<50 and ≥50 years) showed that women <50 years have larger reservoir and conduit LA strain than men <50 years, while in subjects older than 50 years, the sex-related differences were no longer significant.[78]

In the meta-analysis by Pathan *et al.*,[93] only body size and heart rate were significantly associated with LA strain parameters, while age and sex did not show any significant relationship, presumably due to the heterogeneity of the studies involving variable age and sex distribution and relatively narrow age ranges. Moreover, the need of dedicated, nonforeshortened apical views (in contrast to conventional apical four-chamber views optimized for the LV) to obtain LA strain measurements is a relatively recent principle in echocardiography and it is likely that, in many of the previous studies of LA strain, there were no dedicated acquisitions for the LA.

Besides age and sex, LA strain parameters were reported to independently correlate with LV systolic and diastolic function indices (stroke volume, global longitudinal strain, E/A, e′ average velocity).[78,95] The LA conduit and reservoir strain increased, and LA contractile strain decreased with larger magnitudes of global LV longitudinal strain.[78] These relationships confirm the close functional interplay between LA and LV function and the pivotal role of LV longitudinal shortening in determining LA conduit and reservoir function.

Regional differences in LA strain could be potentially useful for evaluation of LA dyssynchrony by 2D STE, as an indirect measure of heterogeneous LA fibrosis and dysfunction that might predict AF recurrence after radiofrequency ablation.[85] Normally, the segments adjacent to the mitral annulus, particularly at the inferior wall, display larger strain values than those at the mid and apical (roof) segments of LA. The lowest values of LA strain are found at the LA roof in the region of the pulmonary vein insertion, where the heart is anchored to the mediastinum.[96] This is presumably related to the fact that in apical views optimized for the LV, the LA is frequently foreshortened and therefore the true LA roof may not be adequately imaged by 2DE.[19] On the other hand, it is also true that reliable measurement of segmental LA strain is challenging, as the LA myocardium is thin and the spatial resolution of 2DE does not allow sufficient detail for adequate regional tracking of the LA wall positioned in the far field in apical views. Moreover, the definition of LA segments is difficult due to varying interpolation across the pulmonary vein and LA appendage orifices. Therefore, despite its theoretical potential, LA regional strain is not currently recommended for clinical application.[65]

Left atrial mechanical dispersion or LA dyssynchrony calculated as the standard deviation of time to peak strain for the LA segments has also been evaluated for both reservoir strain[97] as well as for contractile strain,[85] with both measures demonstrating value in prediction of AF recurrence.

Take-Home Messages

LA Reservoir Strain. Strengths: Uses conventional grayscale four-chamber view, easy to perform and highly reproducible, demonstrated prognostic value, demonstrated diagnostic value in HFpEF, standardized; dedicated software packages are now available.

Weaknesses: Most reference values are obtained with single-vendor equipment by adapting to LA a software package developed for the LV; intervendor variability not yet assessed, independent prognostic value from LV longitudinal strain still to be defined.

LA Contractile Strain. Strengths: Independent of LV function plus all the strengths of LA reservoir strain.

Weaknesses: Prognostic value yet to be demonstrated in large multicenter studies plus all the weaknesses of LA reservoir strain.

LA PRESSURE

The gold standard measurements of LA pressure are those obtained with invasive cardiac catheterization: pulmonary capillary wedge pressure (PCWP), LV pre-A pressure, mean LV diastolic pressure, and LV end-diastolic pressure.[98,99] In clinical practice, PCWP is widely used as an indirect surrogate for LA pressure, with the benefit of avoiding direct measurements through a transseptal approach given its potential risks.[100] However, the invasive nature and the technical challenges that may affect its accuracy are important limitations that restrict the routine use of PCWP measurement to establish diagnoses and address the management of patients in routine clinical practice.

Over the last four decades, Doppler techniques, including both spectral Doppler and TDI, have played a pivotal role in the estimation of LA pressure. Additionally, myocardial deformation imaging has recently developed and proved to be an accurate indirect means for estimating LA pressures.[101,102]

During the reservoir phase, LV systole allows LA cavity enlargement as the mitral annulus moves toward the LV apex, with an initial drop in LA pressure that will increase as the LA cavity starts filling with the systolic component of pulmonary venous flow. The conduit phase reflects LA emptying, as a result of the combined effect of the rebound of the mitral annulus back to its resting level and the suction function of the LV. The resulting early diastolic LA emptying during diastolic pulmonary venous flow and the filling of LV have been used in estimating LA pressure by measuring the isovolumic relaxation time and E wave deceleration time from the pulsed-wave Doppler tracings, albeit with only modest correlation.[103,104] Left atrial pump function is caused by active atrial contraction after electrical depolarization (P wave on ECG), which results in pumping a second stroke volume during atrial systole (i.e., A wave) into the LV. The LA emptying and LV filling components, during early and late diastole (‘E and A waves, respectively’), have been shown to closely correlate with the respective LV myocardial velocities e′ and a′, whether taken at individual segments or as a mean of the commonly assessed four annular segments (i.e., lateral, septal anterior, and posterior).[105,106] In addition, different combinations of these velocities have been reported as potential predictors of LA pressure with varying accuracies, including E/A and E/e′ ratios and the difference between mitral valve A wave duration and the pulmonary venous retrograde A wave duration (indicating raised LA pressure if the difference is >30 msec).

Left atrial linear dimension, area, and volume have also been used to reflect cavity pressure with varying accuracy, with volumes having the highest accuracy. In addition to LA cavity size and flow dynamics, intrinsic LA myocardial function has also been recently reported to reflect cavity pressures. Left atrial myocardial deformation by longitudinal strain and strain rate at different phases of the cardiac cycle—peak atrial longitudinal strain (PALS), peak atrial contraction strain, and total LA EmF—have been reported to correlate with PCWP.[107] Finally, several studies have found a significant correlation between the extent of LA fibrosis (both atrial histology[108] and gadolinium on CMR[109]) and echocardiographically derived LA strain, providing the anatomical bases for the noninvasive assessment of LA compliance.

An isovolumic relaxation time < 40 msec in an elderly breathless patient with normal heart rate is consistent with increased LA pressure, and a zero value suggests LA pressure of 30 mm Hg.[110] An E/A ratio > 2.0 with a short E wave deceleration time < 140 msec in a patient with an enlarged LA is consistent with raised LA pressure. Likewise, E/e′ > 15 suggests raised LA pressure particularly in patients with HF. A recent meta-analysis of 1,343 patients that evaluated the relationship of parameters of LA size and function (by strain analysis) provided a strong association between increased LA size and altered LA function in predicting raised LA pressure.[111] A PALS ≤ 19% proved to be more accurate than the LAVI ≥ 34 mL/m^2 in predicting a raised PCWP (defined as >15 mm Hg), with a sensitivity of 80% versus 75% and similar specificity of 77%. The diagnostic odds ratio (DOR) of PALS ≤ 19% (DOR = 15.1) to predict PCWP > 15 mm Hg was higher than that of LA area > 20 cm/m^2 (DOR = 13.0), LAVI ≥ 34 mL/m^2 (DOR = 10.1), total LA EmF ≤ 35% (DOR = 9.95), or LA diameter ≥ 46 mm (DOR = 5.41). Finally, in the same meta-analysis, an E/e′ ratio ≥ 15 proved to be less accurate than LA cavity size measurements in predicting PCWP, with sensitivity of 64% (52%-74%) and specificity of 56% (44%-68%).

Recently, Singh *et al.*[112] found a gradual decrease of PALS values with worsening LV diastolic dysfunction. Using receiver-operating characteristic analysis, they found three distinct PALS thresholds to identify the various diastolic dysfunction grades (area under the curve, 0.86-0.91). In an independent validation group (n = 139) with a wide spectrum of diastolic function, the diagnostic accuracy of PALS was up to 95%.[112] By replacing the LAV_{max} ≥ 34 mL/m^2 with PALS < 20% in the algorithm proposed by ASE/EACVI to assess LV diastolic function, the accuracy to predict increased LV end-diastolic pressure measured invasively was raised from 72% to 81%.[28,113] The improved accuracy of the new algorithm was confirmed in patients with both normal and reduced LV ejection fraction.[113] In 378 consecutive patients with unexplained exertional dyspnea who underwent invasive cardiopulmonary exercise testing to ascertain the presence of HF with preserved ejection fraction (HFpEF) or noncardiac causes of dyspnea, PALS (29% ± 16% vs 40% ± 13%; P < .0001) and conduit strain (18% ± 10% vs 22% ± 10%; P = .0001) were significantly impaired in HFpEF compared with noncardiac dyspnea. Of all echocardiographic indices, PALS best discriminated HFpEF from noncardiac dyspnea (area under the curve = 0.719, P < .0001), outperforming E/e′ (area under the curve difference = +0.117, P < .0001), LA enlargement (AUC difference +0.090, P = .001), tricuspid regurgitation velocity >2.8 m/sec (AUC difference

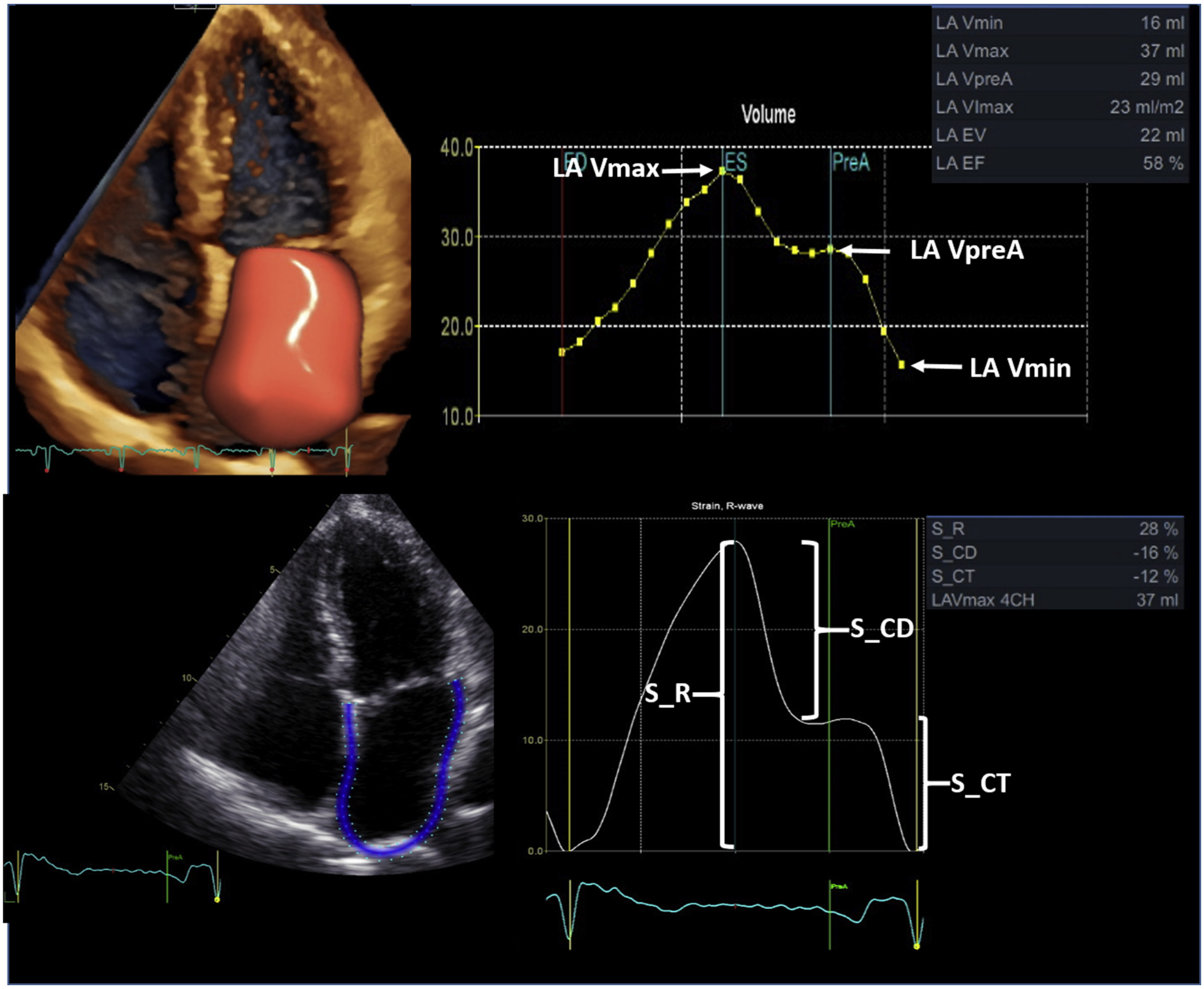


Figure 7 Phasic LA strain using R-R ECG gating illustrating the relationship of LA phasic strain to the ECG and corresponding LA volumes. Left atrial reservoir strain corresponds to LAV_{max} in ventricular systole, while LA conduit strain corresponds to LAV_{preA} in early diastole and LA contractile strain corresponds to LAV_{min} in end diastole. *S_CD*, LA conduit strain; *S_CT*, LA contractile strain; *S_R*, LA reservoir strain.

+0.082, $P = .0085$), LV hypertrophy (AUC difference +0.0159, $P < .0001$), and LV global longitudinal strain (AUC difference +0.0198, $P < .0001$).[114]

In view of the significantly thinner LA myocardial wall compared with that of the LV, the increase in LA size resulting from raised cavity pressure affects myocardial intrinsic properties and overall LA performance. Left atrial systolic function decreases, as shown by reduced myocardial strain and strain rate, and consequently reduced atrial compliance consistent with increased stiffness, as shown by LA stiffness index. The raised stiffness index has been shown to accurately predict compromised exercise capacity in patients with HF.[115]

Take-Home Messages

LA Pressure Estimates. Strengths: All spectral Doppler and LA deformation markers are fairly accurate in predicting raised (>15 mm Hg) LA pressure.

Weaknesses: They are indirect measures with spectral Doppler parameters based on pressure difference between LA and LV. All predictors of raised LA pressure should be taken in combination and in the context of increased LA volume.

PROGNOSTIC VALUE OF LA METRICS

Current recommendations[6] encourage the reporting of the LAV_{max} because there is a large body of evidence supporting LAV_{max} to stratify cardiovascular risk.[79] However, there is recent evidence suggesting that LAV_{min} may be a more important prognostic indicator using either 2DE or 3DE.[2,116] The correlation with LV filling pressures has also been reported to be stronger for LAV_{min} than for LAV_{max}.[117,118]

Although not yet recommended in guidelines, the assessment of LA function could significantly improve the prognostic value of LA metrics in many clinical conditions. It is important to understand the relationship of phasic LA strain to various periods of the cardiac cycle on ECG as well as to LA volumes (Figure 7).

In particular, the relative robustness and easy evaluation of LA strain using 2D STE has recently led to evidence that at least LA reservoir function (i.e., PALS) could be an important prognostic marker particularly in the evaluation of patients with suspected LV diastolic dysfunction and HFpEF.[5,71,113,114]

In patients with AF, the addition of PALS and LAV_{max} to statistical models has been consistently reported as incremental to the $CHADS_2$ score in predicting hospitalization and/or death.[90]

LA FUNCTION IN CLINICAL PRACTICE

Atrial Fibrillation

Reduced LA reservoir and booster pump function were associated with an increased risk of new-onset AF in both the general or cryptogenic stroke populations.[80] In asymptomatic individuals with more than one clinical risk factor for AF, LV global longitudinal strain and LAVI were the strongest predictors of AF occurrence, suggesting their utility for AF prevention.[119] Similarly, LA mechanical dispersion has demonstrated incremental value in predicting future episodes of AF in asymptomatic individuals at risk of HF.[97] Altered LA function was also associated with AF occurrence in otherwise healthy athletes.[84] Studies have demonstrated an association between LA strain, extent of LA fibrosis, cardioembolic events, AF occurrence, or increased hospitalizations.[81,82,109]

Abnormal reservoir function, either measured as PALS by LA strain or 3D LA volumes, was associated with an increased recurrence of AF after catheter ablation procedure.[85-87] Therefore, LA reservoir function might be used for best predicting the success rate of the procedure and to individualize treatment and follow-up.

Left atrial strain has also been demonstrated to improve the current risk stratification for cardioembolism in patients with low CHA_2DS_2-VASc score.[89,90]

In summary, LA reservoir function is a predictor of AF occurrence and recurrence following ablation, with associated value to determine thromboembolic risk. However, large prospective studies are needed to confirm whether LA function can be used to risk-stratify patients in clinical practice.[91,120]

Cardiomyopathies

The value of LAV_{max} is a predictor of the development of HF, irrespective of LV systolic function. In patients with dilated cardiomyopathy, once HF is present, LA enlargement and dysfunction are important predictors of clinical outcomes.[121-123] Similar predictive value for adverse events has been reported in patients with HF of ischemic etiology.[124] The prognostic value of LA function, and especially of LA reservoir function by strain analysis, has been suggested in several observational studies in patients with HF and reduced ejection fraction, particularly in candidates for cardiac resynchronization therapy.[125]

In patients with HFpEF, the relevance of LA volume is perhaps even greater, LAV_{max} having both diagnostic and prognostic value.[126,127] The prognostic value of LA reservoir strain in HFpEF patients has been reported both for patients in sinus rhythm and in AF.[68,128] Overall, the utility and relevance of LA strain seems much greater in HFpEF than for HF with reduced ejection fraction.[129-131]

Heart Valve Diseases

In mitral regurgitation, patients who developed cardiovascular events demonstrated reduced PALS, reduced total LA EmF, larger LAV_{max}, and lower LV global longitudinal strain at baseline.[132,133] The role of LA function assessment to optimize timing of surgery in asymptomatic patients with moderate mitral regurgitation has not been demonstrated yet, but $LAV_{max} > 60$ mL/m^2 has been acknowledged as an important prognostic marker[13] and an indication for surgery in asymptomatic patients with severe degenerative mitral regurgitation by current guidelines.[134,135]

In patients with aortic valve stenosis, guidelines do not recommend the assessment of the LA to address their management.[134,135] Nevertheless, LA dilation is associated with LV remodeling and provides prognostic information in severe asymptomatic aortic valve stenosis.[136,137] A PALS $<$ 21% was an independent predictor of prognosis in patients with severe aortic stenosis.[138] Given the combined influence of LV diastolic and systolic function and of LA performance on systolic pulmonary pressure, the decline of PALS might be considered a marker of global myocardial impairment in patients with aortic stenosis. Further studies are needed to confirm the critical role of LA relaxation in prognosis and to validate its relevance in routine clinical practice.

Finally, PALS was reported to be a univariate predictor of cardiovascular morbidity and mortality at 12 years in 385 patients without AF, HF, and ischemic heart disease who underwent echocardiography as part of the Copenhagen City Heart Study.[139] However, in this study, the prognostic value of PALS was modified by sex; PALS was an independent predictor of outcome in women but not in men.

CONCLUSION

Measurements of the LA have hitherto been limited to evaluation of LAV_{max}. However, there are emerging data to support the role of LAV_{min} and phasic LA volumes as well as LA phasic function, utilizing 2D strain analysis. The particular areas of relevance of LA metrics in the clinical care of patients include evaluation of LV diastolic dysfunction, HFpEF, and AF, all of which are common and growing problems. While more comprehensive normative data and robust evidence of the prognostic utility of the newer techniques including 3DE and strain analysis are warranted, it is likely that evaluation of not only LA volume but LA function parameters will be included in future guidelines for evaluation of patients.

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