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REVIEW

Imaging of the left atrium: pathophysiology insights and clinical utility

Otto A. Smiseth[1], Tomasz Baron [2], Paolo N. Marino[3], Thomas H. Marwick[4], and Frank A. Flachskampf [4,*]

[1]Department of Cardiology, Institute for Surgical Research, Oslo University Hospital, University of Oslo, Rikshospitalet, Oslo N-0027, Norway; [2]Department of Medical Sciences, Cardiology and Clinical Physiology, Uppsala University, Uppsala University Hospital, Uppsala, Sweden; [3]School of Medicine, Università del Piemonte Orientale, Novara, Italy; and [4]Department of Medical Sciences, Uppsala Clinical Research Center, Uppsala University, Ingång 40, Akademiska sjukhus, Uppsala 751 85, Sweden

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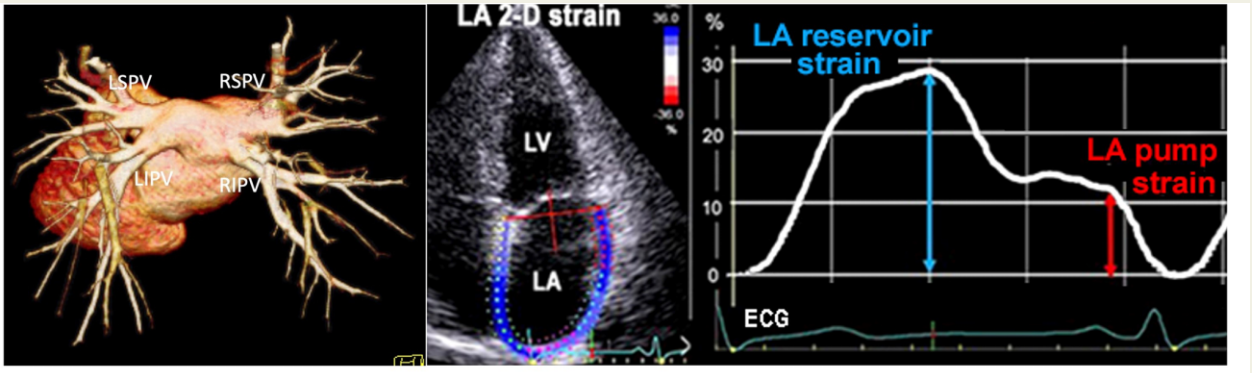
Left atrial imaging and detailed knowledge of its pathophysiology, especially in the context of heart failure, have become an increasingly important clinical and research focus. This development has been accelerated by the growth of non-invasive imaging modalities, advanced image processing techniques, such as strain imaging, and the parallel emergence of catheter-based left atrial interventions like pulmonary vein ablation, left atrial appendage occlusion, and others. In this review, we focus on novel imaging methods for the left atrium, their pathophysiological background, and their clinical relevance for various cardiac conditions and diseases.

Graphical Abstract



Better insights into left atrial morphology (e.g., left panel, by cardiac computed tomography) and function (e.g., right panel, left atrial strain) have become recently available. We review the pathophysiological basis and clinical impact of these features, which provide new diagnostic tools and improved therapeutic guidance for heart failure, mitral regurgitation, stroke risk, and others, as well as for the planning of left atrial interventions.

Keywords left atrium • strain • heart failure • heart failure with preserved ejection fraction • left atrial mechanics • stroke • athlete's heart • atrial mitral regurgitation

*Corresponding author. Tel: +46 70 42 50 725; E-mail: frank.flachskampf@medsci.uu.se.

Introduction

Recent clinical research interest in imaging of the left atrium (LA) has been driven by several developments:

- Recognition of LA remodelling and functional abnormalities as a bellwether and mirror of primarily left ventricular diseases, such as hypertension, heart failure, cardiomyopathies, and others. This was first demonstrated by identifying LA enlargement as a risk factor of future adverse events, perhaps most prominently in the Framingham Heart Study.
- The rise of incidence and prevalence of atrial fibrillation (AF) in an ageing population, together with the emergence of percutaneous (or minimally invasive) interventional AF ablation procedures targeting primarily the ostial portion of the pulmonary veins.
- The introduction of percutaneous LA appendage (LAA) closure as a tool to minimize embolic stroke risk in AF patients unsuitable for anticoagulation.
- The increasing availability of cardiac computed tomography (CT) and cardiovascular magnetic resonance (CMR) with their superior spatial resolution (CT) and tissue characterization abilities (CMR), supplementing echocardiography as the workhorse of routine LA assessment.

Thus, a confluence of secular changes in population age and cardiovascular morbidity distribution, improved interventional options, and enhanced imaging options has brought the LA into the focus of cardiovascular research. In the following, we will provide a brief update on the most important recent insights in this field, while deferring specifics of CMR imaging and peri-interventional imaging to the corresponding parallel review articles in this Focus issue.

The tools of contemporary LA imaging

Echocardiography

Visualization and volume calculation of the LA is part of routine echocardiography. Surprisingly, LA diameter continues to be measured and used in risk calculators, despite good evidence that the LA does not enlarge uniformly.[1] The most important novelty in this modality has been the introduction of strain imaging based on speckle-tracking (see below). Several detailed and comprehensive reviews of standard quantitative echocardiographic evaluation of the LA have been published, and the reader is referred to these documents for technical details.[2–4] 3D echocardiography, especially transoesophageal echocardiography (TOE), has become a standard tool in LA interventions such as closure of atrial septal defects and of the LAA, and also during transseptal puncture for LA or mitral interventions. A rivalling technique, intracardiac echocardiography, uses similar imaging via disposable imaging catheters inserted transvenously, thus avoiding the heavy sedation and/or ventilation necessary if peri-interventional TOE is used. For further details, we refer to the corresponding review article in this issue of the journal.

Cardiovascular magnetic resonance

This topic is addressed in another accompanying review article in this issue of the journal.

Cardiac CT

CT has an excellent spatial and satisfactory temporal resolution, but its use is limited by radiation exposure and the need for iodinated contrast agent. Beyond its established role in coronary artery imaging in patients with low-intermediate pre-test probability of significant coronary stenosis, CT has been extensively used for planning of percutaneous procedures and early detection of their potential complications. Using retrospectively electrocardiogram (ECG)-gated protocols, functional series can be obtained, and similarly to CMR, accurate measurement of myocardial mass, chamber volumes, and ejection fraction, as well as deformation analysis can be performed. With dedicated software, LA functional measures including LA strain can be obtained, but its role in the clinical evaluation has not been established.[5]

In the context of catheter ablation of AF, CCT provides detailed information on LA morphology, pulmonary vein anatomy and thrombus formation in the LA or LAA; see *Figures 1 and 2* and Supplementary data online, *Video S1*. Anatomical variations of pulmonary veins, such as a common PV trunk or additional pulmonary veins are present in approximately one-third of the general population,[6] and detailed knowledge of their anatomy determines success rate of pulmonary vein isolation. CT has shown higher sensitivity and specificity than TOE in the detection of post-procedural pulmonary vein stenoses.

Presence of contrast filling defects within the LAA enables detection of thrombus with overall accuracy of 94%.[7] Importantly, use of additional delayed acquisition images (after 15–30 s) improves differentiating LAA thrombus from contrast mixing artefact (*Figure 2*) and further improves the diagnostic accuracy.[8]

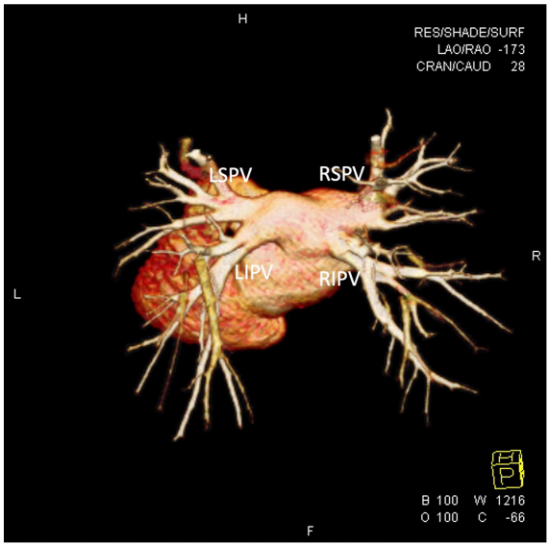


Figure 1 3D volume-rendered reconstruction of a normal left atrium showing a typical configuration of pulmonary veins. See Supplementary data online, *Video S1*. LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein.

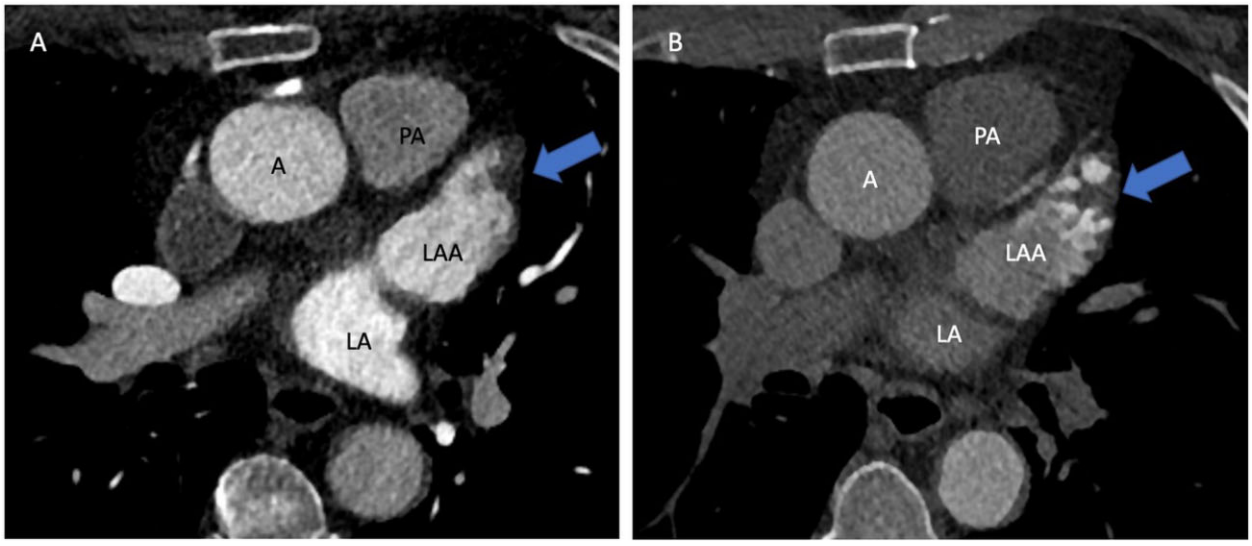


Figure 2 Representative example of early and delayed CT acquisitions for the detection of left atrial appendage thrombus. (*A*) Early scan showing contrast filling defect peripherally in the appendage, suspected to be thrombus (arrow). (*B*) Late phase image shows lingering contrast agent in the LAA and reveals a network of pectinate muscle ridges (arrow), thus excluding thrombus. A, ascending aorta; CT, computed tomography; LA, left atrium; LAA, left atrial appendage; PA, pulmonary artery.

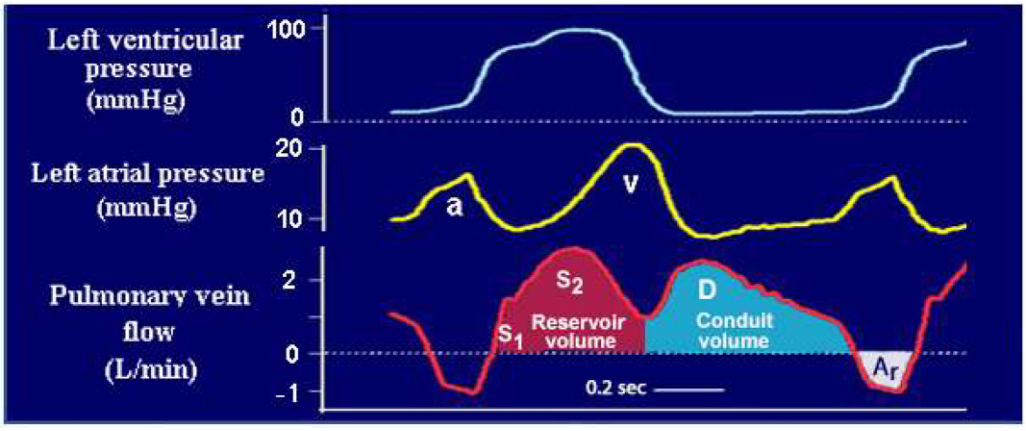


Figure 3 Intraoperative recordings of LV and LA pressures (by micromanometres) and pulmonary venous flow (by flowmetre) in a patient prior to coronary artery bypass surgery. Red and blue coloured areas represent volumes entering the LA as reservoir and conduit volumes, respectively. The area labelled A_r marks flow reversal during LA contraction. Unpublished material from the study by Smiseth *et al.*[20] LA, left atrium; LV, left ventricle.

Left atrial mechanics

The role of the LA is to serve as a reservoir which collects blood from the pulmonary veins during left ventricle (LV) systole, and ejects the collected volume into the LV in diastole. The reservoir volume is ejected in two phases, in early diastole by passive contraction (elastic recoil), and in late diastole by active contraction (booster pump). In addition, the LA serves as a conduit for transport of blood from the pulmonary veins to the LV. The conduit phase starts at mitral valve opening and continues until active LA contraction in sinus rhythm, and until LV end-diastole in patients with AF (*Figure 3*).

The LA reservoir function allows the LV to fill rapidly and at low pressures. This is particularly important during exercise, when diastolic filling time is abbreviated by increased heart rate. In AF, the reservoir function is markedly attenuated due to stiffer atrium[9] and loss of booster pump function. Therefore patients with AF are more dependent on conduit function.[10] Because LV filling with the LA as a conduit implies transport of blood from the pulmonary veins and venules, rather than recruitment directly from the LA, it is a slower mechanism. This may be compensated by elevation of pulmonary venous pressure which increases driving pressure for flow from the

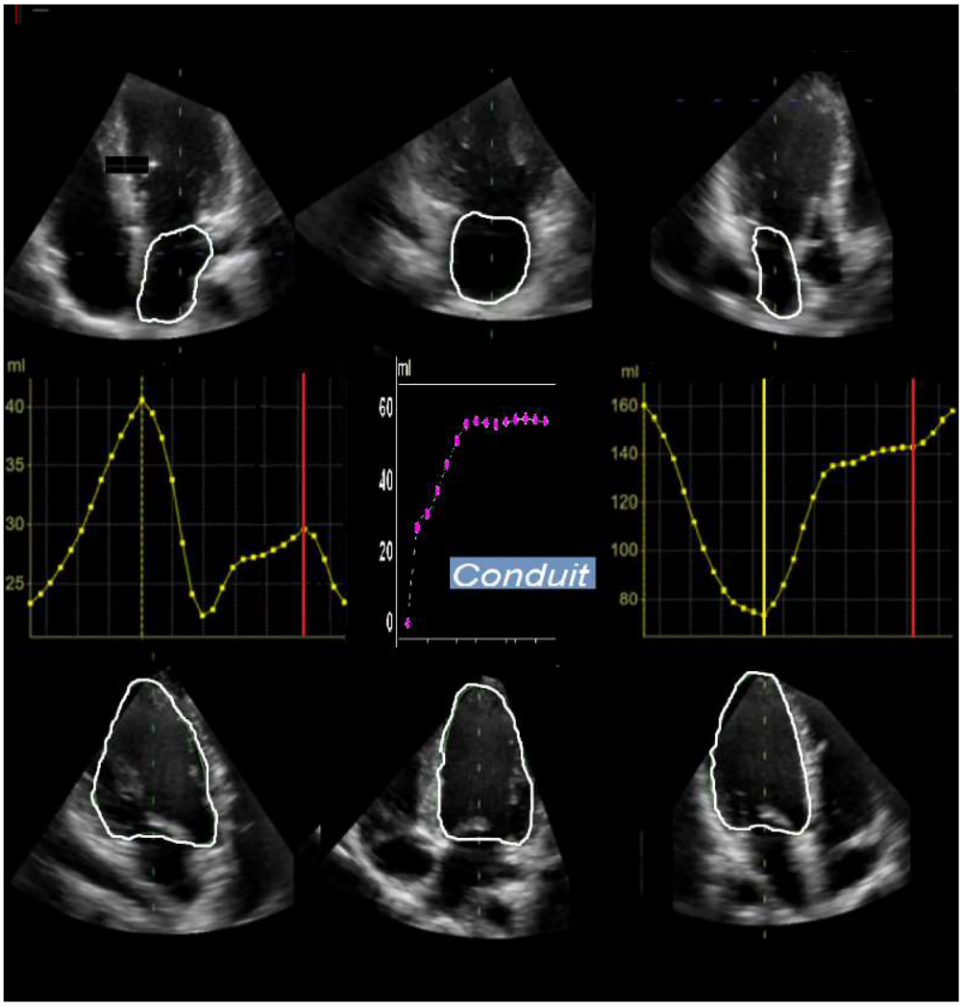


Figure 4 In order to assess atrial phasic function, 3D echocardiography can be used to acquire simultaneously LV and LA volume curves during an entire beat. From these curves conduit volume can be computed (provided mitral and/or aortic insufficiency is trivial) as the integral of the net, diastolic instantaneous difference between synchronized LA and LV volume curves, beginning at minimum LV cavity volume (yellow vertical line) and ending just before atrial contraction (red vertical line), at the time of the peak of the P wave on the ECG. The same time intervals can be used to calculate reservoir and pump volume. Modified, with permission, from Ref.[80] ECG, electrocardiogram; LA, left atrium; LV, left ventricle.

pulmonary veins towards the LV. This is probably one mechanism to explain why patients with AF tend to have elevated LV filling pressures. As shown in a series of studies from the group of Paolo Marino,[11–13] echocardiography may be used for separate quantification of total reservoir volume, booster pump volume and conduit volume. Total LA reservoir volume is calculated as the difference between maximum volume (LAVmax) and minimum volume (LAVmin). The booster pump volume equals the volume prior to atrial contraction minus LAVmin. Left atrial conduit volume can also be measured clinically. By definition, the conduit volume equals LV stroke volume minus (LAVmax-LAVmin), corrected for late-diastolic regurgitation volume into the pulmonary veins.[14] Practically, conduit volume can be calculated from simultaneous LA and LV volume curves by 3D echocardiography (*Figure 4*). In the absence of mitral and/or aortic insufficiency, conduit volume is the difference of the integrals of these volume curves, beginning at the time of minimum LV volume (ventricular end-systole) and ending with atrial contraction,[13] although inertial forces may cause continuation of pulmonary venous inflow beyond the P-wave of the ECG.

Left atrial strain

The most widely used parameters of LA function are the transmitral atrial-induced flow velocity (*A*) and the ratio between peak early mitral velocity (*E*) and *A*. The *A* wave reflects the booster pump function. More recently, LA strain has been introduced as a measure of LA function which allows quantification of both reservoir and booster pump function. Since the conduit volume is passing directly through the atrium and by definition does not imply any change in LA volume or deformation, LA conduit function cannot be assessed by strain imaging.

The clinical standard today is to measure LA strain by speckle tracking echocardiography, which has a feasibility >90%. Note that

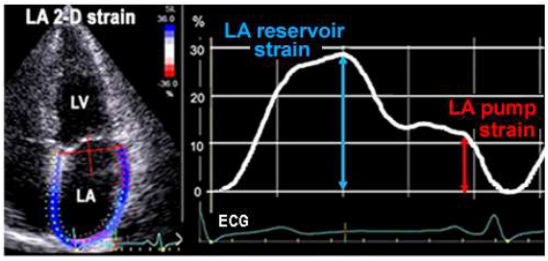


Figure 5 Left atrial strain by speckle tracking echocardiography. Left panel: echocardiographic image (apical four-chamber view) showing the left ventricle (LV) and left atrium (LA) with colour-coded region of interest for LA strain. Right panel: LA strain trace along with ECG. Reservoir strain is indicated by the blue arrow and pump strain by the red arrow. ECG, electrocardiogram.

this parameter measures the 'longitudinal' shortening of the LA walls in a tangential direction to the endocardial atrial border in an apical view.[15] It is also possible to measure LA strain rate by speckle tracking echocardiography, but this measurement is challenging because of the modest temporal resolution of clinical 2D imaging. When measuring LA strain, reservoir strain is calculated from end-diastole, defined by the onset of QRS, until time of maximum LA strain. Pump strain is measured from onset of LA contraction, after onset of the P wave in the ECG at the sharp downslope of the strain trace, to end-diastole (*Figure 5*). It is most practical to report strain values as absolute numbers. As recommended by the joint EACVI/ASE/Industry Task Force,[15] LA strain is measured using a non-foreshortened apical four-chamber view; for further details refer to Ref.16 Computation of LA strain from both apical four- and two-chamber views is an option, but rarely used . Measurements are reported as global longitudinal strain, which is the average value for the entire atrium.

Since the LA wall is very thin (typically ~2–3 mm[17]), separation between subendocardial and subepicardial strain is not feasible. Furthermore, due to the limitation that currently available software extrapolates strain across the entries of the pulmonary veins and across the base of the appendage, measurement of segmental strains is challenging and not yet used routinely. Recent data, however, suggest that LA dyssynchrony, measured as delayed stretch of the LA lateral wall relative to atrial septum, predicts response to cardiac resynchronization therapy.[18]

Similar to the LV, LA function is determined by its preload (Frank–Starling mechanism), afterload and contractility. Left atrial preload is represented by pre-A LA pressure, although pericardial pressure represents a substantial fraction of LA intracavitary pressure.[19,20] Analogous to the LV, where afterload is represented by arterial pressure and stiffness, LA afterload is represented by LV end-diastolic pressure and stiffness. The afterload dependency implies that elevation of end-diastolic pressure and stiffening of the LV lead to reduction in LA pump strain. Furthermore, reduction in LA contractility, as in atrial myopathy, or atrial stunning following atrial arrhythmia are associated with low values of LA pump strain.

Mechanistically, LA reservoir strain (LARS) is tightly coupled to LV longitudinal shortening, since the two chambers are anatomically connected, and in systole, the LV thereby exerts a direct stretching effect on the atrium. This is an important contributing mechanism to reduced LARS in patients with systolic dysfunction. Furthermore, LA pressure as reflected in pulmonary capillary wedge pressure, is another independent determinant of LARS. The dependency of LA strain on filling pressure probably reflects both LA remodelling in chronic heart failure, and an immediate stiffening effect by elevated LA distending pressure. The contractility of the LA is also a modifier of LARS since more vigorous LA contractions, causing enhanced pressure rise, is followed by more marked decline in LA pressure which increases pulmonary venous return. This mechanism accounts for the S1 wave in the pulmonary venous flow trace (*Figure 3*). Finally, for geometric reasons, LA strain is a function of LA volume. This is because strain is a relative measure, and a large atrium requires less stretch to accommodate a given reservoir volume.

Figure 6 shows associations between LA reservoir and pump strain and their determinants.[9] For reservoir strain, LV GLS and LV filling pressure were strongest determinants, with GLS slightly stronger than filling pressure. Left atrial volume was also an independent determinant of LARS, but much weaker than LV GLS and filling pressure. Pump strain showed essentially similar association with LV GLS and filling pressure. These observations are in keeping with findings in a number of earlier, smaller studies.[21–23]

Left atrial strain may be used clinically for assessment of LV filling pressure, and to differentiate between heart failure with preserved ejection fraction (HFpEF) and non-cardiac disease.[2,9,24,25] Left atrial reservoir strain may also be used to assess prognosis and it appears to provide information which is superior to the LA maximum volume index.[26,27] Recent studies have shown that LA strain had a stronger correlation with invasive LV filling pressure than LAVi, and in the most recent EACVI consensus document on imaging in HFpEF, LA strain is recommended as an additional parameter for evaluation of LV filling pressure.[28] In a large multicentre study with invasively measured filling pressure as reference, it was shown that LARS was comparable to, but no better than the traditional indices mitral *E*/*e*′ ratio, peak tricuspid regurgitation velocity and LAVi as marker of filling pressure.[9] The recommendation in the last EACVI consensus document[28] is to use LA reservoir strain as the third parameter when one of the three other criteria is missing and the remaining two are inconsistent (*Figure 7*). In the study by Inoue *et al.*,[9] the optimal cut-off to differentiate between normal and elevated LV filling pressure was 18% for LARS when defining PCWP >12 mmHg as elevated, and 16% when using PCWP ≥15 mmHg, or LVEDP ≥16 mmHg as alternative of elevated LV filling pressure. One limitation of using LARS for the assessment of LV filling pressure is that accuracy depends on LV EF and is best when EF is reduced.

Average values for LARS decrease slightly with age and average normal values in healthy individuals are reported in the range 36–47%, with lowest values in the elderly.[29] The lower limit of normality of LARS is vendor and age-dependent, but values <19–23% are considered abnormally low.

There is also clinically useful information in LA pump strain, which is comparable to reservoir strain as marker of filling pressure. The

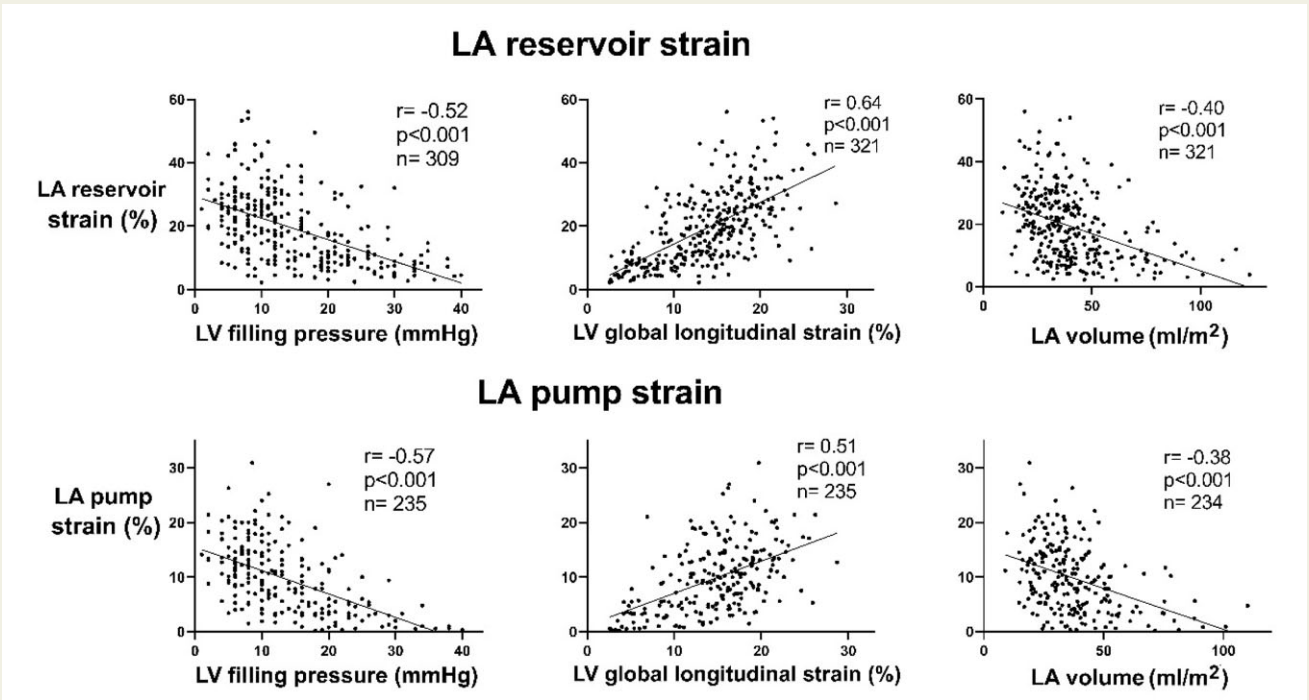


Figure 6 Determinants of LA strain: relationships between LA reservoir strain (upper panels) and pump strain (lower panels) and their determinants. Data from a multicentre study of 322 patients with cardiovascular disease of different aetiologies. See text for further details. Reproduced, with permission, from Ref.[9] LA, left atrium.

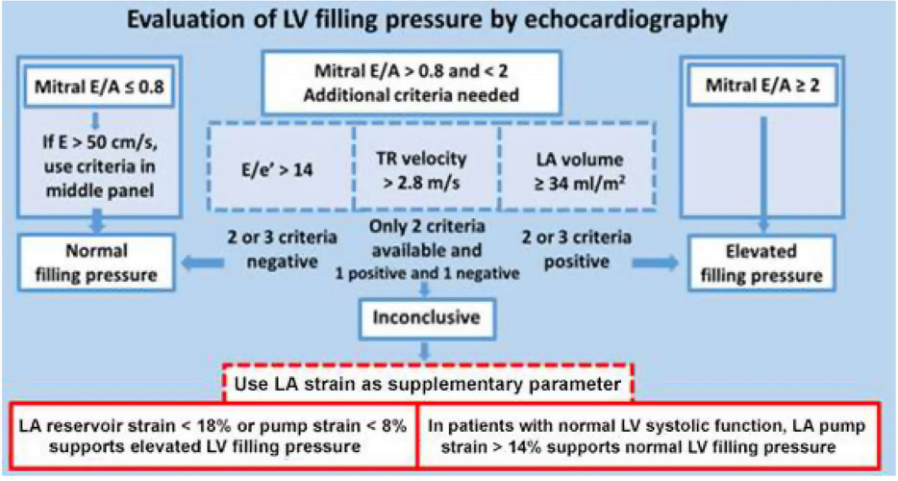


Figure 7 Algorithm for estimation of LV filling pressure. Modified from the last EACVI consensus document (31) by including LA pump strain in addition to reservoir strain. Based on study by Inoue *et al.*[9] LA, left atrium; LV, left ventricle.

signals are of lower amplitude, however, and when there is tachycardia it is difficult to identify the appropriate signals. The best cut-off value for 'pump strain' to differentiate between normal and elevated LV filling pressure was 8%.[9] Furthermore, pump strain >14% was an excellent marker of normal filling pressure (*Figure 6*).

Taken together, the results from a large number of clinical studies indicate that imaging of LARS is ready to be implemented as a diagnostic method in clinical routine. When used alone or in combination with LAVi, LARS provides useful information regarding LV filling pressure and appears to be a useful risk marker.

Recent insights into LA pathophysiology and its clinical relevance

Hypertension, aortic stenosis, and left ventricular hypertrophy

LA volumes increase and functional indices like LARS decrease over time in patients with arterial hypertension. In fact, LA enlargement is considered a form of end-organ damage in hypertension, and is a predictor of AF and of ischaemic stroke, the latter even in patients with preserved sinus rhythm. Aortic stenosis, another form of LV pressure overload, has similar consequences on LA size and function; LA enlargement is an independent predictor of adverse events in patients with aortic stenosis in sinus rhythm.[30] Left ventricular hypertrophy, which regularly accompanies hypertension or aortic stenosis, additionally accelerates LA remodelling by contributing to increased diastolic LV stiffness and impaired diastolic function. Importantly, antihypertensive therapy has shown beneficial reverse remodelling effects on the LA both in animal and clinical studies: ACE inhibitors and angiotensin receptor blockers have been shown to affect a decrease in LA volumes and an improvement in functional indices. The same is true for intervention in severe aortic stenosis.

Heart failure

Filling pressure

The accurate assessment of diastolic dysfunction (DD) and LV filling pressure are both critically important. The same three parameters (left atrial volume, transmitral flow and annular velocity) have been used for diastolic evaluation for a couple of decades, and despite the recommendations of learned societies,[31] many clinicians struggle with the assessment of diastolic function. As detailed in the section on LA mechanics, there is a reasonably strong, invasively well-validated correlation of LA reservoir (and pump) strain with LV filling pressures, and LA strain has now been proposed as a reserve parameter in the guideline-recommended approach to non-invasive estimation of these pressures. A reasonable argument can be made in support of left atrial strain as a component of diastolic evaluation, based on the association of LARS with left ventricular filling pressure in a number of studies.[9,21,32] In patients with heart failure risk factors, left atrial strain correlates with both conventional invasive and non-invasive markers of filling pressure.[32] Because LARS has a linear relationship with LV filling pressure, some investigators have proposed that it can be used to assign grades of DD, with normal corresponding to LARS >35%, grade 1 DD to LARS of 25–35%, and grade 2 DD to LARS <25%.[33] The LA demonstrates little reverse remodelling in heart failure, so LA enlargement can persist after LA pressure have normalized. This inconsistency contributes to the large number of patients identified as having indeterminate diastolic function. In contrast, the LARS does revert to normal with normalization of LA pressure. When LARS <25% was used in place of LA volume index (LAVI) >34 mL/m^2, there was a 75% reduction in indeterminate diastolic function—all being recategorized as normal (*Figure 8*).[33]

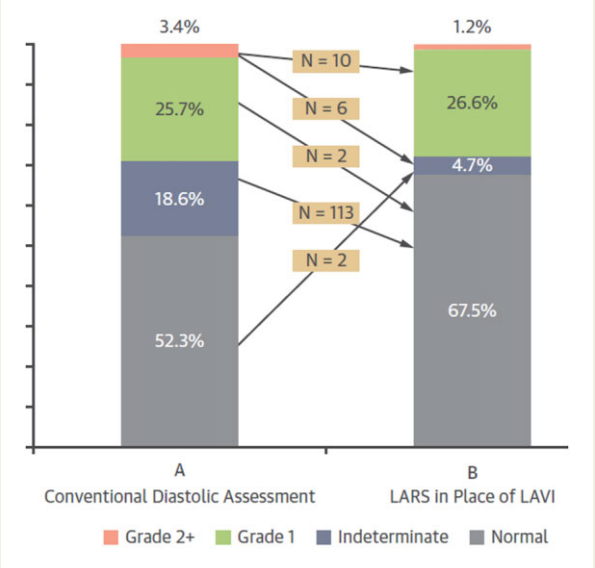


Figure 8 Comparison of diastolic function grades by grading methods. Reassignment of diastolic function from using conventional (ASE/EACVI) diastolic function recommendations to LA reservoir strain (LARS) used in place of LA volume index (LAVI). Total number of individuals in A is 758 and in B is 738 (the number in which LARS measurement was feasible). Numbers in boxes are absolute numbers of individuals changing group. Reproduced, with permission, from Ref.[33] LA, left atrium.

Stage B heart failure

The development of heart failure is preceded by a subclinical phase, during which the patient has abnormal cardiac structure and function, but no symptoms.[34] These patients with 'Stage B' heart failure (SBHF) have a higher risk than patients with heart failure risk factors with normal cardiac structure and function. The challenge is the recognition of SBHF, the guideline definition of which conforms to the previously dominant heart failure with reduced ejection fraction (HFrEF) phenotype. Recent studies have proposed that GLS and DD be added,[35] but it would be simple to add LARS as well. In support of this, the risk evaluation of patients with heart failure risk factors is facilitated by both LARS[32] and the categorization of DD based on LARS.[33] The presence of LARS < 24% has a 2.9-fold increased hazard of incident heart failure, after adjustment for clinical and echocardiographic markers.

Heart failure with preserved EF

Although >50% of heart failure is now attributable to HFpEF, the diagnosis of this entity remains challenging. The H2FPEF score (based on age, body mass index, antihypertensive therapy, presence of AF, pulmonary artery pressure, and E/e') is designed for euvolaemic patients with unexplained exertional dyspnoea.[36] The HFA-PEFF process involves a clinical step followed by biomarkers and echocardiographic features (e', E/e', LAVi, LVMI, relative wall thickness, TR velocity, and LVGLS).[37] Given the limitations of assessing LV filling pressure from E/e',[38] the use of LARS might be a useful addition. The use of LARS has shown better correlation with pulmonary capillary wedge pressure than standard parameters such as E/e' and LAVI.[39] In fact, LARS (OR = 0.71, P = 0.049) was associated with HFpEF, independent of BNP (OR = 1.08, P = 0.025), and LAVI (OR = 1.59, P = 0.04), and LARS <17.5% was 89% sensitive, albeit not very

specific, for the clinical diagnosis of HFpEF.[40] When HFpEF was defined by an elevated pulmonary capillary wedge pressure response to exercise, LARS <33% was 88% sensitive and 87% specific.[24] The aspect of atrial function that is most strongly associated with aerobic capacity in HFpEF is controversial.[41,42]

In addition, LARS is predictive of outcomes in HFpEF. A substudy of the PARAMOUNT trial showed that left atrial function by strain imaging was impaired in patients with HFpEF, compared with controls, even after adjusting for confounders.[42] In fact, left atrial strain was associated with heart failure hospitalization and AF in HFpEF.[42] Likewise, in the TOPCAT study, 52% of HFpEF patients had abnormal LARS, and this was associated with the primary composite endpoint (CV death, heart failure hospitalization, and aborted sudden death), as well as heart failure hospitalization.[43] Observational studies have shown LARS to provide incremental prognostic information to traditional risk factors and LVGLS.[27]

Heart failure with reduced EF

Left atrial strain is significantly impaired in HFrEF. Abnormal LARS is associated with increased LV filling pressure in patients with a moderately and severely reduced LVEF.[22] Consistent with the notion that increased filling pressure explains the reduction in LARS, this parameter is associated with heart failure, irrespective of whether it is HFrEF or HFpEF,[44] and LARS is similarly predictive of heart failure onset in both heart failure phenotypes.[45] Moreover, as in HFpEF, LARS is associated with exercise capacity[46] and prognosis.[47] LA strain improves with treatment response—in particular showing an improvement in cardiac resynchronisation therapy responders, in contrast with a deterioration (presumably reflecting increased filling pressure) in non-responders.[48]

Athlete's heart

In athletes, the LA regularly dilates and about half of elite athletes have an enlarged LA[49]; a meta-analysis[50] found an average increase in indexed LA volume compared with non-athletic controls of 37%. LA strain parameters are decreased in athletes with dilated LA.[50,51] This is at least in part explainable by pure geometric reasons: since LA volume increases, less percentage increase of LA volume and thus longitudinal strain is necessary to accommodate a given stroke volume during systole, analogous to the observation of low-normal or mildly decreased left ventricular ejection fraction and global longitudinal strain in athletes. However, impaired strain might not be purely a benign consequence of changed LA geometry. Impaired LA strain, in particular reservoir strain, has been implied as a predictor of AF, for example after AF ablation,[52] but this relation not been specifically studied in the context of athletic LA remodelling.

Table 1 Normal ranges of reservoir, conduit and contractile function using echocardiographic speckle tracking (mean and 95% confidence intervals)[71] and CMR feature-tracking[72]

	Reservoir	Conduit	Contractile
Echo	39.4 (38.0–40.8)%	23.0 (20.7–25.2)%	17.4 (16.0–19.0)%
CMR	22.6–29%	8.7–21%	7.8–14%

CMR, cardiovascular magnetic resonance.

Atrial mitral regurgitation

Progressive atrial enlargement is a fundamental consequence of substantial chronic mitral regurgitation of any cause, and portends an impaired prognosis in both primary and secondary mitral regurgitation.[53,54] Recently, however, attention has been drawn to the reverse mechanism: mitral regurgitation may be caused by atrial enlargement alone, most often in the context of chronic AF, and sometimes, chiefly in HFpEF, even without AF. In patients with atrial MR, the mitral annulus enlarges, in particular posteriorly, and the antero-posterior annulus diameter increases. Mitral annular area enlarges and its cyclic contraction decreases. If this enlargement is not matched by corresponding compensatory mitral leaflet growth,[55–57] leakage through the mitral valve ensues, generating typically a central regurgitation jet. This pathomechanism, which has an analogy on the right side in atrial tricuspid regurgitation, has only recently received adequate attention. The prevalence of moderate or severe purely 'atrial' mitral regurgitation in patients with AF overall is low and in the 5% range,[57,58] and severe mitral regurgitation is rare, since by definition the LV is not dilated. It has been shown[57] that mitral leaflet area in these patients is insufficient to ensure a 'watertight' closure of the valve: the ratio of diastolic mitral leaflet area to systolic mitral annular area was on average 1.6 in normals and patients with AF but no more than mild MR, while it was 1.3 in patients with AF and moderate or severe MR. Restoration of sinus rhythm has been shown to reduce severity of MR and LA volume.[58]

Role of LA enlargement and AF for stroke and arterial embolism

Atrial enlargement increases the risk of arterial embolism including stroke, both in sinus rhythm[59] and in AF.[60] Conversely, reverse atrial remodelling after successful ablation procedures reduces this risk. Similarly, functional indices like minimal LA volume, LARS or LA ejection fraction all predict embolism and recurrence of AF. Of note, LARS independently (of LA volume and of clinical factors except age) predicted AF and stroke in a population-based sample of patients <65 years.[61] Conversely, an increased probability of 'hidden' (subclinical) paroxysmal AF episodes in cryptogenic stroke patients has been shown for those with impaired LARS.[62,63] Additional well-established risk factors for LA thrombus formation and embolism are the presence of spontaneous echo contrast in the LA and low peak flow velocities (<20 cm/s) in the LAA, as well as LAA volume itself. Further, morphology of the LAA, best assessed by CT, seems to play a role in embolic risk, with the common 'chicken-wing' morphology conferring the lowest risk compared with other variants ('cauliflower', 'windsock', 'cactus'[64]). TOE continues to be the imaging modality of choice to assess embolic risk and can be supplemented or replaced if necessary by contrast CT.[65] CMR imaging of the LA and LAA can add to stroke risk stratification by identifying LA fibrosis through late gadolinium enhancement. The latter was strongly associated with stroke independently of clinical predictors, like the $CHADS_2$ score, in a retrospective study of 387 patients.[66]

Table 2 Human studies of LA remodelling in hypertension and diastolic dysfunction

Dernellis *et al.*[77]	**ACEI ± diuretic vs. controls**	**Decrease in LA reservoir volume (35.4–29.3 mL); increase in LA conduit volume (43.8–51.3 mL)**
Mattioli *et al.*[78]	Telmisartan at baseline and 1 year	Decrease in maximum LA volume (35 ± 5–32 ± 5 mL)
Tsang *et al.*[79]	ACEI vs. placebo	Reduction in LAVI by 9.7 mL/m^2

CMR, cardiovascular magnetic resonance; LA, left atrium; LAVI, LA volume index.

Table 3 Causes of LA enlargement

Related to pressure or volume load	Arterial hypertension
	Mitral valve disease
	Aortic valve disease
	Physical training/athletics
	Shunt lesions: atrial septal defect, ventricular septal defect, anomalous pulmonary venous drainage, open ductus arteriosus Botalli, intrapulmonary or other systemic shunts (e.g. in Paget's disease), dialysis shunts
Related to myocardial disease	Heart failure with left ventricular diastolic dysfunction/HFpEF/HFrEF
	Left ventricular cardiomyopathies (especially dilated, hypertrophic, non-compaction)
Related to storage diseases and expansion of the extracellular myocardial volume	Cardiac amyloidosis, (Anderson-)Fabry disease, haemochromatosis, etc.
Related to arrhythmias	Atrial fibrillation, atrial flutter, atrial tachycardias
Congenital	Cor triatriatum, shunt lesions (see above under "related to pressure and volume load")
Errors in measurement	E.g. inclusion of atrial septal aneurysm, LA appendage into LA volume

These aetiologies are not mutually exclusive, but several mechanisms may enhance each other in their effect on the LA (e.g. aortic stenosis associated with cardiac amyloidosis, atrial fibrillation, and mitral regurgitation).
HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LA, left atrium.

LA reverse remodelling

Left atrial remodelling is defined as a persistent change in LA size or function,[67] which usually occurs in response to chronic LV myocardial disease (e.g. heart failure and ischaemic heart disease), pressure or volume overload conditions (hypertension, valvular heart disease, particularly mitral valve disease), or atrial arrhythmia. Remodelling can be distinguished into electrical (including arrhythmic triggers and pathways for re-entry), functional (changes in function without an initial increment in size), and structural (involving fibrosis and enlargement). These may occur in sequence or independently. The magnitude of remodelling depends on the severity and duration of exposure, as well as the aetiology. Acute remodelling, for example within a week of exposure to a stressor, is usually reversible, but chronic remodelling is more likely to be irreversible. An excellent and detailed review on the subject has been published a few years ago.[68]

The challenge with clinical application of the concept of LA remodelling is predominantly one of the definition and measurement reliability. Absolute criteria are justifiable based on population norms for LA volume,[69] and function by echocardiography[70] and CMR[71] (*Table 1*). Similar cutpoints have been validated by outcomes—LAVI >34 mL/m^2 being associated with double the hazard of progressing from paroxysmal to persistent AF and LARS <31% with a 3.97-fold increase in hazard.[72] Relative changes in LA size and function are also potential risk markers—a 15% change of LA volume has also been used as a marker of structural remodelling,[73] but although the degree of functional change that is associated with this (19 ± 8–22 ± 9%) exceeds the lack of response in patients without reverse remodelling, it is small and within the confidence intervals of serial measurement. The most useful cut-off of all need to account for the test–retest variability of structural and functional parameters varies according to the technique being used—for volumes, the small mean differences with CMR[74] a 3D- and 2D-echocardiography[75] belie test–retest variation that leads to smallest detectable changes of the order of 14 mL. For LA function, the test–retest variability of echocardiographic strain is not well defined, but for CMR strain it is significant, probably ~12%.[74,76] Direct measurement of LA fibrosis is challenging, and assessment of its change over follow-up is difficult.

Examples of studies showing LA remodelling in response to antihypertensive therapy are given in Table 2.[77–79] The outcomes show relatively minor changes of LA volume, which although different from control groups, lie within the confidence intervals of re-measurement. Moreover, although the observed changes are statistically significant, the clinical importance of changes of <10 mL are questionable. In summary, although LA reverse remodelling is an important physiologic signal to distinguish patient groups, it seems challenging to apply this to track the progress of individual patients.

Practical consequences

In the following, we try to provide advice regarding imaging features of the LA for routine clinical practice, structured as responses to frequently asked questions.

Q. Which parameters of LA structure and function should be measured in routine echocardiography?

A. LA maximal (LV end-systolic) volume should be measured in every patient, preferentially by biplane Simpson's method. Attention should be paid to non-foreshortened views, which often do not coincide with the best views for the LV. Volume from a single 'good' view is preferable to biplane volume where one view is clearly suboptimal. Indexation to body surface area is standard, but in obese patients 'overcorrects' LA volume and thus may lead to underestimation of LA size.

Calculating LA longitudinal reservoir or peak strain is useful especially to assess DD, HFpEF, or elevated LA pressure. In particular, LA strain may replace non-obtainable or ambiguous other fundamental diastolic function parameters.[28] Although LA pump strain theoretically is a superior parameter of LA function than reservoir/peak strain, in many studies pump strain does not provide independent additional diagnostic or prognostic information to peak LA strain.

Q. What importance has the finding of an enlarged LA without obvious aetiology (e.g. valvular heart disease or cardiomyopathy)?

A. LA enlargement is a frequent finding. Table 3 displays differential diagnoses to consider. In a broad sense, there are two—not mutually exclusive—main pathophysiologic pathways to consider:

- LA enlargement due to chronically elevated LA pressure. This, in turn, suggests either elevated diastolic LA and LV pressures due to diastolic LV dysfunction or some degree of mitral valve disease, usually regurgitation, or both. LV DD may not necessarily be evident on echocardiography at rest, since current algorithms, even if LA strain is included in the evaluation, are not very sensitive to DD.[9]
- LA enlargement due to AF, which may be paroxysmal or subclinical.
- Also consider an unrecognized shunt, underestimated mitral regurgitation, or errors in tracing (like inclusion of an atrial septal aneurysm or LAA).

Q. In AF, which information on long-term durability of sinus rhythm after cardioversion can be obtained from LA imaging (irrespective of other important factors like duration of previous AF)?

A. Apart from LA volume per se, decreased LA strain and low transmitral A velocity are independent predictors of AF relapse.

Q. Which imaging features of the LA inform about thromboembolic risk?

A. Apart from increased LA volume per se, presence of spontaneous echo contrast in the LA or LAA (by TOE), low LAA flow velocity (average peak value < 20 cm/s), and LAA morphology imply increased embolic risk. Naturally, presence of thrombus or sludge in the appendage is a strong thromboembolic risk factor.

Q. Can monitoring of LA volume or function be used to steer therapy, e.g. of heart failure?

A. This is not known. Although it is plausible that LA size and function will change in parallel to pressure and volume load of the LA, it is not clear that reverse remodelling happens in a way that it could be used routinely for therapeutic monitoring. Remodelling is affected by possibly irreversible or only partially and slowly reversible 'fibrotic' atrial myocardial changes which may persist despite optimal therapy. On the other hand, if reverse remodelling or improvement in LA function (increase in strain) is found, this indicates improved physiology and prognosis.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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