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THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Left Atrial Structure and Function, and Left Ventricular Diastolic Dysfunction

JACC State-of-the-Art Review

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ABSTRACT

Defining left atrial (LA) function has recently emerged as a powerful parameter, particularly in evaluation of left ventricular (LV) diastolic dysfunction (LVDD) and heart failure with preserved ejection fraction. Echocardiographic assessment of LVDD by echocardiography remains a challenging task; recent recommendations provide a simpler approach than previous. However, the shortcomings of the proposed approach (including transmitral flow, tissue velocity, maximum left atrial volume [LAV], and estimated pulmonary artery systolic pressure), lead to the presence and severity of LVDD remaining undetermined in a significant proportion of patients. Maximum LAV is a surrogate measure of the chronicity and severity of LVDD, but LAV alone is an insensitive biomarker of early phases of LVDD, because the LA may take time to remodel. Because the primary function of the LA is to modulate LV filling, it is not surprising that functional LA changes become evident at the earliest stages of LVDD. Moreover, LA function may provide additive value, not only in diagnosing LVDD, but also in grading its severity and in monitoring the effects of treatment. The current review provides a critical appraisal on the existing evidence for the role of LA metrics in evaluation of LVDD and consequent heart failure with preserved ejection fraction. (J Am Coll Cardiol 2019;73:1961–77) © 2019 the American College of Cardiology Foundation. Published by Elsevier. All rights reserved.

Left ventricular (LV) diastolic dysfunction (LVDD) is highly prevalent, but remains difficult to characterize. The original recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging (ASE/EACVI) were complex, and discordances between multiple parameters led to variations among observers (1). The 2016 ASE/EACVI recommendations are simpler and may be more accurate (2), but fail to classify a large number of patients (3,4). The question is whether transmitral flow, tissue velocity, maximum left atrial (LA) volume (LAV), and estimated pulmonary artery pressure are sufficient to diagnose LVDD.

Maximum LAV has emerged as an important biomarker for adverse cardiac events in a variety of cardiovascular conditions (5), and is an established surrogate for the severity and chronicity of LVDD (2). In addition to size, LA function provides estimates of structural and functional adaptive changes that may

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ABBREVIATIONS AND ACRONYMS

2DE = 2-dimensional echocardiography

3DE = 3-dimensional echocardiography

AF = atrial fibrillation

ASE = American Society of Echocardiography

EACVI = European Association of Cardiovascular Imaging

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

LA = left atrial/atrium

LAV = left atrial volume

LV = left ventricle/ventricular

LVDD = left ventricular diastolic dysfunction

TDI = tissue Doppler imaging

help to characterize LV diastolic function, especially during exercise, when the LA may contribute significantly, up to one-third, to total cardiac output (6). Indeed, adaptive LA functional changes become evident with worsening LV systolic and diastolic function (7). This review focuses on the evaluation of LA size, LA function, and LA phasic function, and their specific role in evaluation of LVDD as well as consequent heart failure (HF) with preserved ejection fraction (HFpEF).

HIGHLIGHTS

- LA function, measured as LA reservoir strain, is an important metric in diagnosing LVDD, grading its severity, and monitoring the effects of treatment.
- LA volume has been used as a surrogate of the chronicity and severity of LVDD. However, volume is an insensitive biomarker of the early phases of LVDD.
- LA phasic function can be assessed both by volumetric analysis, using 3-dimensional echocardiography, and by strain/strain-rate analysis, using speckle-tracking echocardiography. The latter is less affected by loading conditions.
- Measurement of LA function improves the diagnostic accuracy and prognostic value of both LVDD and HFpEF algorithms. LA strain provides a feasible biomarker of LA function.

PHYSIOLOGY AND PHASIC FUNCTION OF THE LA

The LA is a dynamic structure. LA function has 3 phases, serving as a reservoir in systole, as a conduit in early diastole, and as a booster pump in late diastole (8) (**Figure 1**). There is a close interaction between LA and LV function in each phase of LA function. LA reservoir function represents LA relaxation and compliance, modulated by LV systolic function through descent of the LV base (8,9). LA conduit function is reliant on LV diastolic function, including both the suction force dependent on LV relaxation and LV chamber stiffness, whereas LA booster function is based on intrinsic LA contractility and LV end-diastolic compliance and pressure (10,11). In normal subjects, the absence of LA contraction (as occurs in patients who develop atrial fibrillation [AF]), is associated with an approximately 20% to 30% decrease in LV stroke volume. This effect will be even more clinically relevant in patients with impaired LV function, as is often demonstrated by symptomatic decompensation in HF patients who develop AF.

Volumetric evaluation of LA phasic function is derived from measurements of maximum, minimum and LA volume immediately before atrial contraction. More recently, LA strain analysis has been used to evaluate LA phasic function. The invasive assessment of LA phasic function using the LA pressure relationship (**Figure 2**) is the gold standard, but is impractical for routine clinical use. (12).

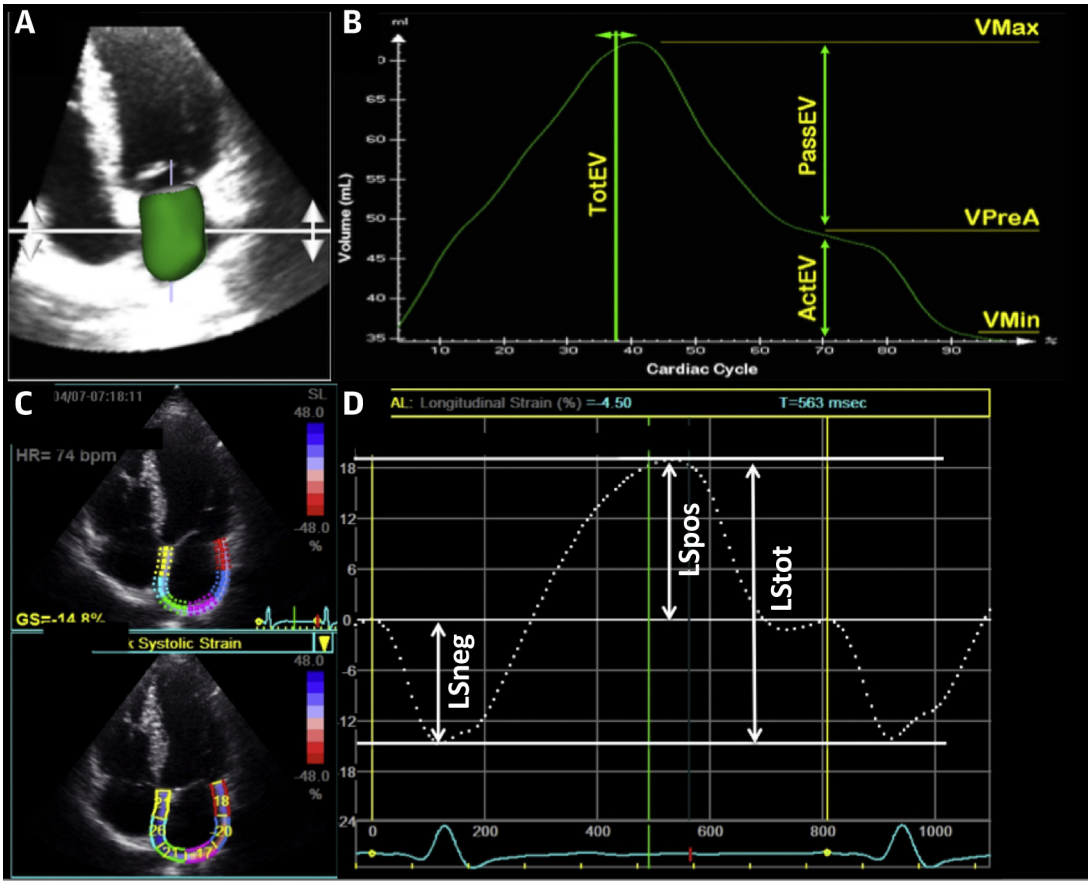
LA SIZE. Increased LA size is an established marker of LVDD (2,7). Because LA enlargement is nonuniform, a biplane LAV (limit of normality of 34 ml/m^2 for both sexes) by either the disk summation or area-length methods (13) is more accurate than previous descriptors of LA size (LA diameter and area), and is a more robust predictor of cardiovascular events (14).

Although most studies reporting the prognostic use of LA size have measured the maximum LAV, recent studies have provided growing evidence that the minimum LAV should also be evaluated. This stands to reason because minimum LAV perhaps better reflects LV end-diastolic pressure, because during diastole (with the mitral valve open), the LA is continuously exposed to LV pressure. Indeed, minimum LAV has been reported to better reflect LV filling pressure and elevated pulmonary wedge pressure, with greater prognostic value, than maximum LAV (15-17).

Due to geometric assumptions about LA shape and foreshortening of the LA cavity in the apical views, LAV measured with 2-dimensional echocardiography (2DE) is often underestimated, when compared with LAV measured by 3-dimensional echocardiography (3DE), cardiac magnetic resonance, or computerized tomography (18,19). Moreover, maximum and minimum LAV measured by 3DE has independent and incremental prognostic value over 2DE LAV (15,17,20,21). Normative values for 3DE LAV have been reported in relatively small numbers of subjects (18,22,23). However, it seems that 3DE LAV are significantly larger than 2D measurements even in healthy subjects, with different upper limits of normality (**Table 1**).

LAV can be also measured by cardiac magnetic resonance and computerized tomography (24). The cost/effectiveness and the added clinical value of using either cardiac magnetic resonance or computerized tomography, instead of echocardiography, to measure LAV remains to be demonstrated. Currently, the use of computerized tomography is limited to an

FIGURE 1 Measurement of LA Phasic Function



Measurement of LA phasic function by volumetric method using 3-dimensional echocardiography **(A and B)** and by strain method using speckle-tracking echocardiography **(C and D)**. Three-dimensional surface rendering of the LA volume **(A)**. LA volume curve over a cardiac cycle, from which the volumetric parameters of the LA phasic function are obtained **(B)**. Color-coded longitudinal LA strain in apical 4-chamber view **(C)**. LA global longitudinal strain using the P-wave on the electrocardiogram as the zero reference time point **(D)**. ActEV = active emptying volume; LA = left atrial; LSneg = negative longitudinal strain; LSpos = positive longitudinal strain; LStot = total longitudinal strain; PassEV = passive emptying volume; TotEV = total emptying volume; VMax = maximal left atrial volume; VMin = minimal left atrial volume; VPreA = atrial volume immediately before atrial contraction.

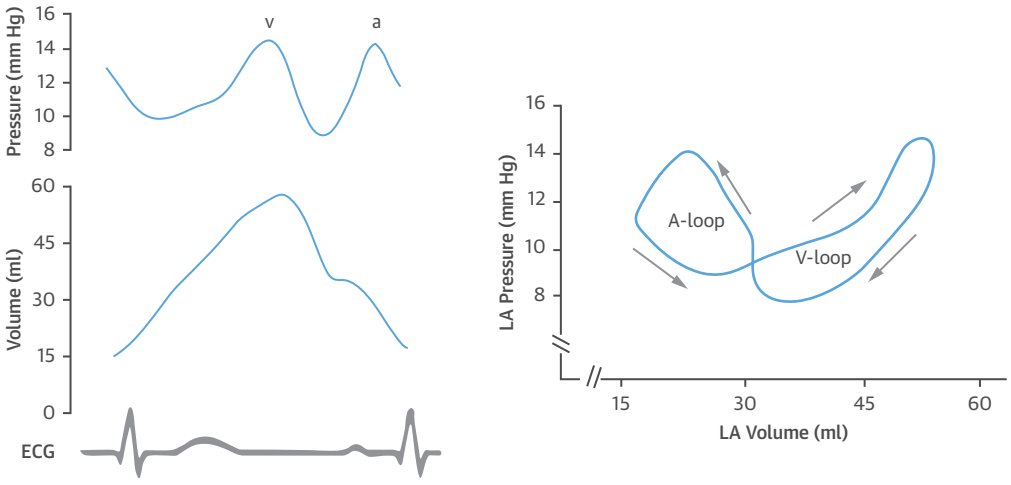
important adjunctive role in the assessment of the LA in AF patients undergoing pulmonary vein ablation procedures. However, echocardiographic evaluation of LA function currently remains integral to evaluation of diastolic function as will be detailed later in the text.

LA PHASIC FUNCTION. Echocardiography is the most frequently used imaging modality to assess LA phasic function (**Figure 2**). LA phasic function can be assessed by volumetric analysis using 3DE, when all volumes can be measured from a single volume trace. Volumetric LA phasic function can be obtained by measuring the maximum (at LV end-systole), minimum (at LV end-diastole), and immediately before atrial contraction (before atrial systole, i.e., before the electrocardiographic P-wave) volumes (**Figure 3**). From these volumes, total, passive and active emptying volumes and fractions can be derived (**Table 2**). Small studies have reported "normal values" for LA phasic function parameters, but there are no reference values obtained from a large population (25).

Alternatively, phasic LA function can be derived from either tissue Doppler imaging (TDI) or 2-dimensional speckle-tracking measurement of longitudinal LA strain and strain rate (12). **Figure 1** demonstrates volumetric and strain-derived LA phasic function.

Theoretically, spectral Doppler assessment of LA filling and emptying flow velocities and velocity-time integrals reflect phasic function. However, these

FIGURE 2 Instantaneous Changes of LA Pressure and LA Volume



Instantaneous changes of left atrial (LA) pressure and left atrial volume (LAV) during 1 cardiac cycle in a normal subject **(left)**; LA pressure–volume relationship composed of the A loop, representing the LA pump function, and the V loop, representing the reservoir function of the LA **(right).** Reproduced with permission from Rosca et al. (12). ECG = electrocardiogram.

parameters are heavily dependent on heart rate, rhythm, and loading conditions, and are currently seldom used. Doppler assessment of pulmonary venous flow has also been used to obtain the S velocity (reservoir function), the D velocity (conduit function), and the pulmonary venous reversal velocity (booster pump function), but successful evaluation requires good quality spectral Doppler tracings. Contrast agents can be used to enhance pulmonary vein flow Doppler signal in patients with suboptimal tracings with not-enhanced Doppler acquisitions.

LA FUNCTIONAL PARAMETERS BY SPECKLE TRACKING AND TDI. Strain and strain rate measure the extent and the rate of myocardial deformation, respectively (26). Both can be measured using either TDI or 2-dimensional speckle-tracking echocardiography (27,28). Conventionally, negative strain relates to myocardial contraction (shortening) and positive strain to myocardial relaxation (elongation). However, for simplicity, in this review, we refer only to the absolute strain value during systole or diastole.

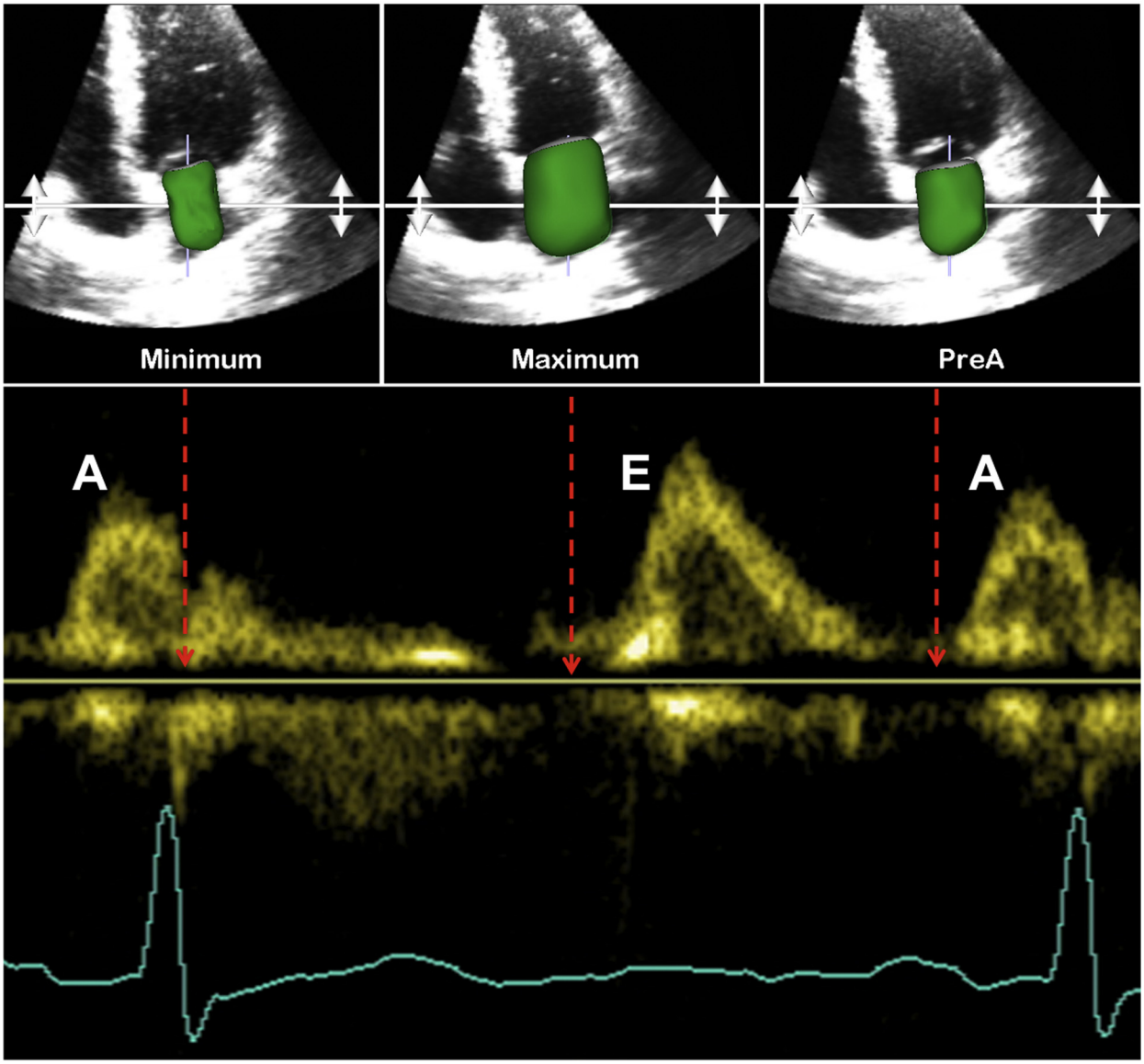
TABLE 1 Phasic Functions of the LA

Phasic Function	Parameter	Computation
Global function: reservoir	Total emptying fraction	$(LAV_{max} - LAV_{min})/LAV_{max}$
Reservoir	Expansion index	$(LAV_{max} - LAV_{min})/LAV_{min}$
Conduit	Passive emptying fraction	$(LAV_{max} - LAV_{preA})/LAV_{max}$
Booster pump	Active emptying fraction	$(LAV_{preA} - AV_{min})/LAV_{preA}$

LA = left atrium; LAV_{max} = maximal left atrial volume; LAV_{min} = minimal left atrial volume; LAV_{preA} = left atrial volume immediately before atrial contraction.

TDI assessment of LA strain. TDI-derived velocities, strain, and strain rate have been applied to the evaluation of global and regional LA function (29). Measurement of myocardial velocity shows that the motion of the LA and LV are concordant due to the tethering of LA tissue by the stronger contraction of the LV. However, LA strain imaging shows that longitudinal shortening and lengthening specific to the function of the LA are discordant compared with LV longitudinal motion because the atrium fills during ventricular systole and empties during ventricular diastole (27,30). The technical challenges of TDI-based strain rate imaging are not trivial, because the technique is susceptible to both translational motion (and hence requires tracking with the motion of the wall), and because it is Doppler-based technique, it is influenced by the insonation angle, so only the walls rather than the roof of the LA can be interrogated, using a long and thin (10 × 2-mm) sample volume (27). Nonetheless, in expert hands, feasibility is high (30). About 10 years ago, from published reports based on TDI-based atrial strain, systolic and early diastolic atrial strain rate were reported to predict the maintenance of sinus rhythm following cardioversion (31,32), and radiofrequency ablation for AF (33). TDI-derived LA strain showed abnormalities in diabetes

FIGURE 3 **Phasic Volume Changes of the LA and Their Relationships With Transmitral Flow**



Phasic volume changes of the left atrium (LA) **(top)** and their relationships with transmitral flow during LA emptying into the ventricle **(center)** and electrocardiogram **(bottom)**. The **red dashed lines** show the timing of various measurements of LA volumes. A = transmitral A-wave velocity; E = transmitral E-wave velocity; Maximum = maximal left atrial volume; Minimum = minimal left atrial volume; PreA = atrial volume immediately before atrial contraction.

(34), hypertension (35), myocardial infarction (36), HF (37), and AF (38), all conditions associated with LVDD.

Speckle-tracking measurement of atrial strain. Though the process of measuring strain by 2-dimensional speckle-tracking echocardiography is relatively straightforward, methodological variations have contributed to variation of the reported normal ranges. These variations include the selection of which apical views were used (4-chamber view only, or both 4-, and 2-chamber views, or all 3 apical views), timing of initial zero reference point (either the onset of the P-wave or QRS complex) (**Figure 4**), and inclusion/exclusion of the roof of the LA. A recent report from the joint EACVI/ASE/Industry Task Force has proposed a process of sharing technical specifications of the software packages designed to post-process

TABLE 2 Reference Values for LA Size and Function by Echocardiography

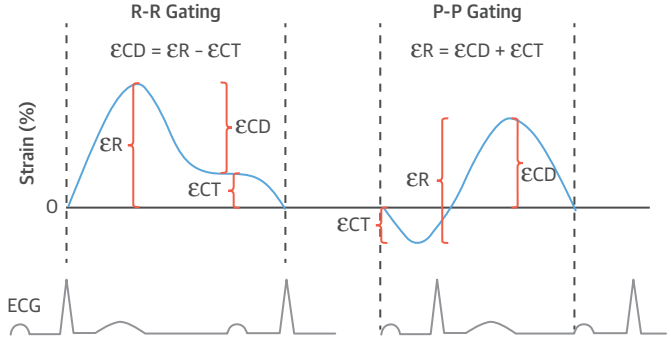
	Left Atrial Size and Function				
	3DE	2DE	p Value	NL 3DE	NL 2DE
Maximal volume, ml/m^2	32 ± 4	24 ± 6	<0.001	<46	<34
Minimal volume, ml/m^2	11 ± 3	8 ± 3	<0.001	<17	<14
PreA volume, ml/m^2	18 ± 5	15 ± 5	<0.001	<28	<25
Total emptying volume, ml	38 ± 10	29 ± 7	<0.001	–	–
Passive emptying volume, ml	25 ± 7	17 ± 6	<0.001	–	–
Active emptying volume, ml	14 ± 6	12 ± 4	<0.001	–	–
Total emptying fraction, %	67 ± 6	69 ± 9	<0.05	>55	>51
Passive emptying fraction, %	44 ± 9	41 ± 10	<0.001	>26	>21
Active emptying fraction, %	39 ± 10	47 ± 10	<0.05	>19	>27
Positive longitudinal strain, %		20.6 ± 6			>11.2
Negative longitudinal strain, %		−14.5 ± 2.3			<−10.2
Total longitudinal strain, %		35.1 ± 5.9			>23.7

Values are mean ± SD unless otherwise indicated.
2DE = 2-dimensional echocardiography; 3DE = 3-dimensional echocardiography; LA = left atrium; NL = normal limit; PreA = immediately before atrial contraction.

2DE datasets for LA measurements (39). The range of normal values of LA reservoir strain (which varies from 30% to 58% in individual studies) (40-42) was addressed in a meta-analysis of 30 studies (2,038 healthy subjects) (43). The normal value of reservoir strain (ε R) was 39% (95% confidence interval: 38% to 41%) (**Figure 5A**), whereas that for contractile strain (ε CT) was 18% (95% confidence interval: 16% to 19%) (**Figure 5B**). Heterogeneity was due to the proportion of female participants, sample size, and zero reference point selection, but race, imaging views, and vendors were not found to account for variation.

The normal ranges are much higher than the LA strain levels associated with disease. For example, increased LV filling pressure was predicted optimally by peak LA strain cutoff <20% (44). Likewise, the best predictors for maintenance of sinus rhythm post-ablation were LA septal and inferior wall peak systolic strain rate of >2.25 s^{-1}, and an inferior wall strain of >19.5% (45). Despite the fact that LA strain is not completely load-independent, loading conditions seem to have less effect on LA strain than LA volume (46).

FIGURE 4 Morphology of the LA Strain Curve Using P-P and R-R Gating

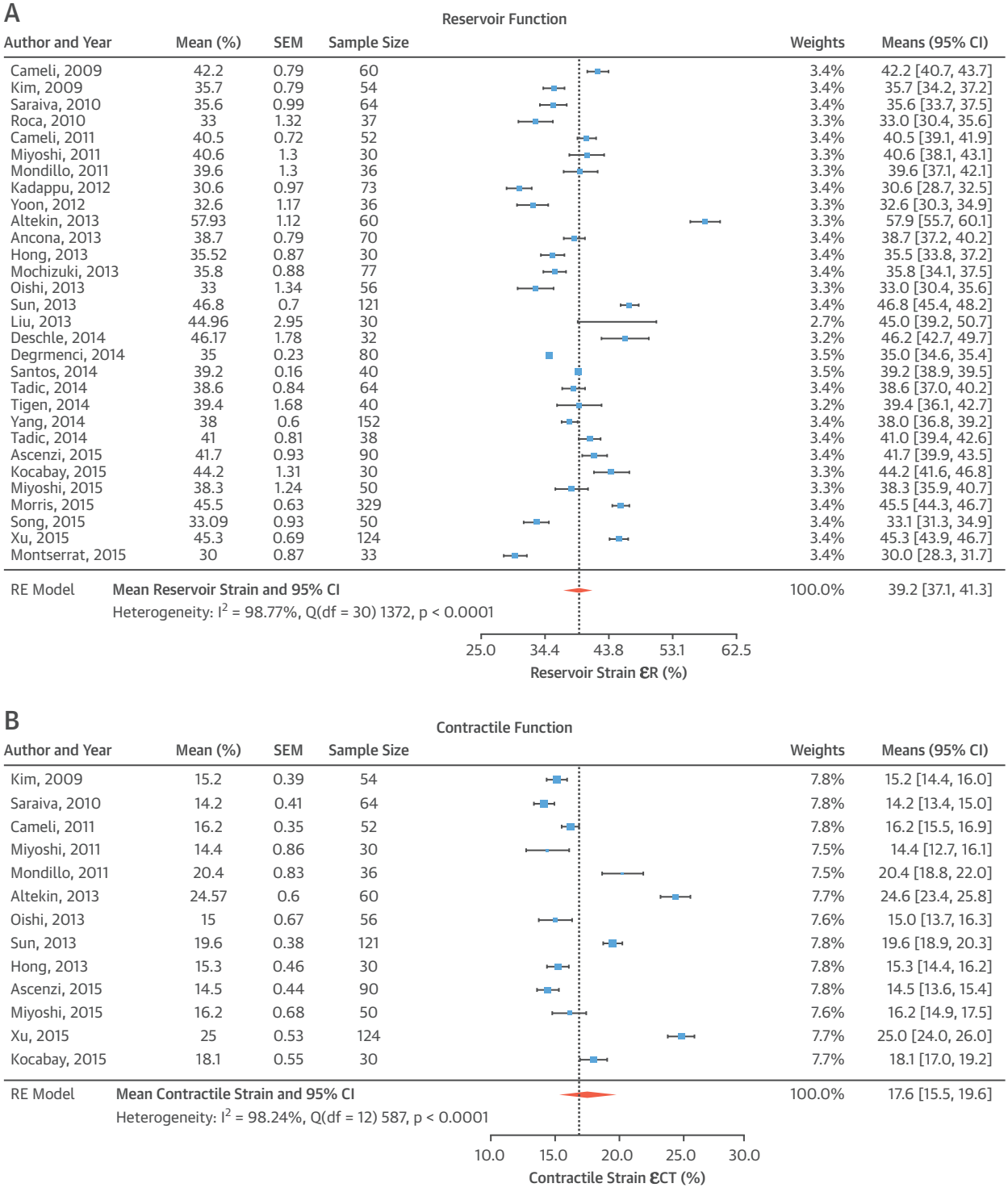


Components attributable to reservoir, conduit, and contractile strain are labeled. ε CD = conduit strain; ε CT = contractile strain; ε R = reservoir strain; LA = left atrial. Reproduced with permission from Pathan et al. (43).

LA TISSUE CHARACTERIZATION. LA dysfunction is thought to result from LA fibrosis, and several biological factors have been implicated in this process (47). Delayed enhancement cardiac magnetic resonance imaging is the gold standard and has been particularly used in patients with AF (48,49). More recently, echocardiographic LA functional alterations have been correlated with LA fibrosis. LA strain inversely correlates with the extent of fibrosis determined by delayed enhancement magnetic resonance imaging (48,49). Following catheter ablation, the incidence of AF recurrence was decreased, with improved LA functional recovery and higher LA strain in patients with limited scar. A histological study demonstrated an inverse correlation between LA strain and extent of histological fibrosis in patients with mitral regurgitation (50). LA strain has also been used to evaluate reversal of fibrosis with various therapeutic agents including spironolactone, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers in animal models (51-53). Thus, although the current evidence is limited, LA strain may be a marker of LA fibrosis, although loading conditions also need to be considered (46).

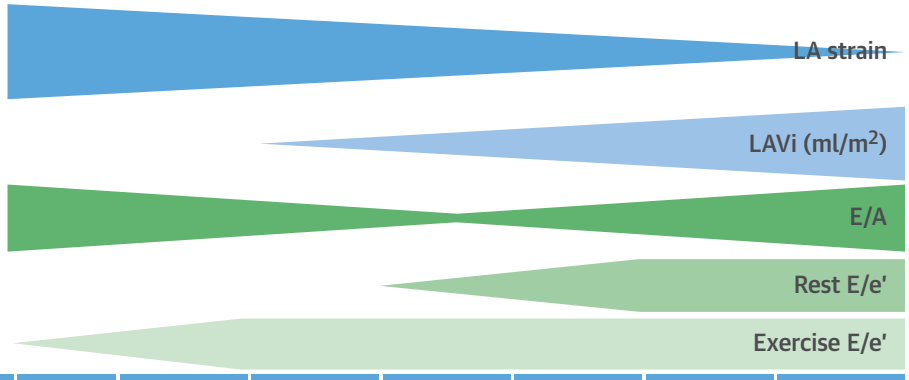
LA COMPLIANCE. Structural and functional LA remodeling is often a consequence of altered LV

FIGURE 5 **Distribution of Normal Ranges of LA Strain in the Published Reports**



Separate forest plots are provided for reservoir strain **(A)** and contractile strain **(B)**. CI = confidence interval; other abbreviations as in Figure 4.

CENTRAL ILLUSTRATION **Evolution of LV Diastolic Parameters With Increasing Disease Severity**



	Normal	Early St1	Late St1	Early St2	Late St2	Early St3	Late St3
LA strain	>35%	24-35%	24-35%	19-24%	19-24%	<19%	<19%
LAVi (ml/m^2)	<34	<34	34-42	34-42	42-48	42-48	>48
E/A	0.8-1.5	<0.8	<0.8	0.8-1.5	0.8-1.5	>1.5	>1.5
Rest E/e'	<10	<10	<10	10-15	>15	>15	>15
Exercise E/e'	<12	<12	>12	>12	>12	>12	>12

Thomas, L. et al. J Am Coll Cardiol. 2019;73(15):1961-77.

Some parameters pseudonormalize, others change late in the disease, or change early and do not progress. LA strain appears to progressively worsen with increasing severity. Moreover, the addition of LA strain may allow more accurate judgment of disease stage. Although cutoffs vary within the published reports and between laboratories, the relative changes are consistent. LA = left atrial; LAVi = indexed left atrial volume; LV = left ventricular.

function and consequent elevated LV filling pressure. LA structural and functional adaptation provides an important compensatory mechanism, at least in the early stages of LVDD, to preserve cardiac output. However, a stage of "decompensation" is reached with resultant reduction in LA compliance. Progressive LA dysfunction with replacement fibrosis will eventually result in an increase in LA pressure and consequent LA failure. This stage in the progression of LA dysfunction with loss of LA compliance could represent a key factor leading from LVDD to the development of HFpEF. Using TDI-based LA strain, an index of "LA stiffness" was derived as a ratio of LA systolic strain to LA pressure (determined invasively as pulmonary capillary wedge pressure and noninvasively as E/e′). The LA stiffness index was able to differentiate between patients with HF with reduced ejection fraction (HFrEF) and HFpEF, but more importantly, between patients with HFpEF and those with LVDD without HF (54). However, such studies have never been replicated using speckle-tracking echocardiography.

LV DIASTOLIC DYSFUNCTION

LVDD is an independent predictor of all-cause mortality in the general population, even in the preclinical stage (55), and evidence of LVDD is required for the diagnosis of HFpEF (56,57). Hence, the accurate evaluation of LVDD is increasingly important in routine clinical practice. Cardiac catheterization is the gold standard to evaluate LV diastolic properties and LV filling pressures; however, invasive assessment is impractical in routine clinical practice. Given the complexity of diastole in itself and the many interrelated factors that influence it, no single echocardiographic parameter can be used in isolation to make the diagnosis of LVDD (3). Instead, an integrated algorithm incorporating multiple parameters, including indexed LAV, e′, E/e′, and tricuspid regurgitation velocity, is currently recommended (2). However, Doppler-derived parameters provide an instantaneous snapshot of LV diastolic function, which may change acutely with changing loading conditions. Although structural alterations such as LAV provide robust information on the chronicity and

TABLE 3 Summary of Studies of LA Metrics in Patients With LVDD

First Author, Year (Ref. #), N, Mean Age	Clinical Setting	LA Parameter	Correlations Between LA Parameter and LVDD	Relation of LA Parameter to CV Risk and Disease Burden
Tsang et al., 2002 (7) N = 140, 58 ± 19 yrs	Referred for clinically indicated TTE in sinus rhythm	M-mode LA dimension, 2D LA volume max	LAVi max correlated with LVDD grade ($p < 0.001$; $r = 0.78$), better than M-mode LA dimension ($r = 0.48$)	CV risk score, congestive HF, vascular disease, TIA or stroke, and smoking history independently related to LAVi max
Pritchett et al., 2005 (63) N = 2,042, ≥45 yrs	Cross-sectional sample of Olmsted County, Minnesota, residents	2D LA volume max	LAVi max good sensitivity and specificity for severe (grade III or IV) LVDD vs. all other grades of DD (AUC = 0.97 [0.94-0.99]), and vs normal diastolic function (AUC = 0.98 [0.96-1.0])	Both DD grade and LAVi max predictive of all-cause mortality. Adjusting for age, sex, EF, and DD grade, LAVi was not associated with all-cause mortality
Hammoudi et al., 2014 (58) N = 90, 59 ± 11 yrs	Patients with resting septal E/e′ <15 referred for exercise stress echocardiography in sinus rhythm, with no atrial arrhythmias or valvular heart disease	2D LA volume max	2D LAVi max measured at rest predicted an abnormal exercise LVFP (defined as E/e′ >13 during exercise) (AUC = 0.85)	NA
Caselli et al., 2010 (21) N = 178, 57 ± 16 yrs	Patients in sinus rhythm, without valve disease, referred for a clinically indicated TTE for LV function	2D, 3D LA volume max/min	3D LAVi min had the best correlation with E/Em ratio ($r = 0.40$; $p < 0.001$) followed by LAVi max ($r = 0.29$; $p < 0.001$)	3D LAVi min was the best independent predictor of major adverse cardiovascular events. (HR: 1.217; 95% CI: 1.075-1.378; $p = 0.002$)
Singh et al., 2019 (44) N = 76, 64 ± 14 yrs (derivation n = 26) 61 ± 12 yrs (validation n = 50)	Patients referred for a clinically indicated left heart catheterization (preA wave diastolic pressure), with a spectrum of LV function	2D STE peak LA strain	Peak LA strain demonstrated better agreement with the invasive measurements of LVFP (81%) than the guidelines algorithm (72%)	NA
Huynh et al., 2015 (61) N = 195, 64 ± 14 yrs	Retrospective; patients in sinus rhythm with atrial dilation (>68 ml for men, >62 ml for women) referred for echocardiography	2D LAVI max, 2D STE peak LA strain	Changes in LVFP (E/e′) associated with LA strain and predicted normalization of LA strain independent of changes in LAV	NA
Brecht et al., 2016 (71) N = 449, 51 ± 14 yrs	Women with and without preclinical LVDD from urban population, in sinus rhythm, without significant valvular disease, normal LVEF	2D LAV max, 2D STE peak systolic strain, LA conduit strain and LA contraction strain	LA reservoir and conduit function, significantly lower in the presence of LVDD. LA reservoir as well as conduit strain more discriminative in detecting early DD vs. LAVI	NA
Singh et al., 2017 (3) N = 90, 64 ± 7 yrs	LV ejection fraction (EF) ≥50%, normal sinus rhythm, and no significant valvular heart disease (i.e., > mild regurgitation or stenosis) or a prosthetic valve	2D LA volumes (max, min, and preA), 2D STE peak LA strain	LAVi increased with worse DD, (grade 2 vs. grade 3 DD = NS), i.e., LAV appears to plateau. 2D STE peak LA strain demonstrated a steady decrease with worsening DD severity, with significance between all DD grades	NA
Morris et al., 2018 (4) N = 517, 68 ± 13 yrs	Patients in sinus rhythm with risk factors and preserved LVEF (LVEF >50%)	2D LAV max, 2D STE peak LA strain	Abnormal 2D STE LA strain significantly associated with elevated estimated PCWP, even with normal LAVI	

2D = 2-dimensional; 3D = 3-dimensional; AUC = area under the curve; CI = confidence interval; CV = cardiovascular; DD = diastolic dysfunction; EF = ejection fraction; HF = heart failure; HR = hazard ratio; LAVi = indexed left atrial volume; LV = left ventricular; LVDD = left ventricular diastolic dysfunction; LVEF = left ventricular ejection fraction; LVFP = left ventricular; NA = not applicable; NS = not significant; PCWP = pulmonary capillary wedge pressure; pts = patients; STE = speckle-tracking echocardiography; TIA = transient ischemic attack; TTE = transthoracic echocardiography; other abbreviations as in Table 2.

severity of LVDD, LAV is not purely determined by LV diastolic function and may be confounded in particular instances with a coexistent LA myopathy.

LA SIZE IN THE ASSESSMENT OF LV DIASTOLIC FUNCTION. In the absence of other causes (e.g., mitral valve disease, AF, bradycardia, high-output states, and so on), LA enlargement reflects LVDD and the chronic, long-term elevation of LA pressure. In the early phases of grade I LVDD, the LAV can still be normal, but as LA pressure increases consequent to the increasing severity of LVDD, the LA cavity dilates. In patients with LVDD and normal LV filling pressures at rest, increased LAV can predict the increase in LV filling pressure during exercise (58). The advantages of using LAV to assess LVDD relate to its feasibility and reproducibility, and maximum LAV is

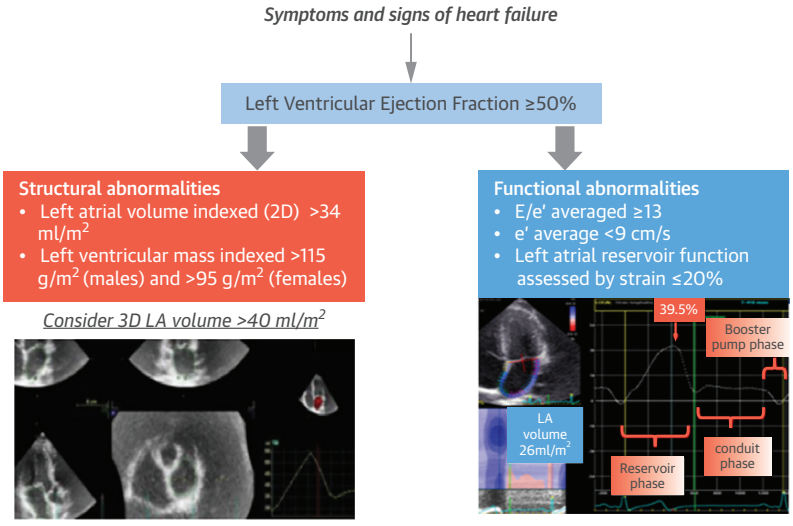
TABLE 4 Summary of Studies With Evaluation of LA Metrics With Provocation

First Author, Year (Ref. #)	N	Provocation	LA Parameter	Finding
Tan et al., 2010 (72)	HFpEF = 50, HT = 15, control = 30	Symptom-limited treadmill exercise	Color TDI A′ velocity (average septal + lateral)	A′ velocity similar at rest in all 3 groups. A′ velocity lowest in HFpEF post-exercise. A′ velocity augmented least in HFpEF pts with exercise
Kusunose et al., 2012 (73)	Unselected patients = 486	Symptom-limited treadmill exercise	2D LA strain	Total LA strain (i.e., reservoir + contractile strain) best correlate of %predicted METS. Lower LA strain associated with higher exercise E/e′
Obokata et al., 2013 (37)	HFpEF = 40, HT without HF = 40	Leg lifts	2D LA strain reservoir and booster	Blunted increase in LA reservoir and booster strain in HFpEF pts
Sugimoto et al., 2017 (82)	HFrEF = 49, HFpEF = 20, healthy controls = 32	Symptom-limited cycle ergometer exercise test	2D LA strain and LA SR-a	LA strain increased most with exercise in controls, blunted in HFpEF, and no increase in HFrEF

av = average septal + lateral; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HT = hypertension; METS = metabolic equivalents; SR-a = contractile strain rate; TDI = tissue Doppler imaging; other abbreviations as in Tables 2 and 3.

currently considered superior to other echocardiographic markers, being increasingly used in large randomized clinical trials (59,60). Among the limitations, LAV can increase despite normal LV diastolic function in patients with bradycardia, high-output states, atrial arrhythmias, or significant mitral valve disease, or in trained athletes (2). LAV can also be unreliable in patients in whom HF therapy results in normalization of LV filling pressure. LA dilatation persists despite improved LV filling pressure, and in such instances, tricuspid regurgitation velocity or LA strain may be used as estimates of elevated LA pressure (2,3). It is therefore important to bear in mind that LA structural "reverse remodeling" is slow and often incomplete (61), with LAV reflecting the legacy of previously elevated filling pressure. Reversibility of LA remodeling is controversial; the duration and extent of altered LVDD that will result in irreversible LA remodeling remain unknown. Although improvement of LA function and reverse atrial remodeling

FIGURE 6 Diagnostic Algorithm of HFpEF: Value of Left Atrial Assessment



Structural and functional abnormalities of the left ventricle and left atrium need to be comprehensively evaluated in HFpEF patients. 2D = 2-dimensional; 3D = 3-dimensional; HFpEF = heart failure with preserved ejection fraction.

TABLE 5 Summary of Studies of LA Metrics in HFpEF

First Author, Year (Ref. #), N, Mean Age	Clinical Setting	LA Parameter	Main Results	Conclusions
Liu et al., 2018 (81) N = 55 HFpEF, N = 31 DD, N = 33 controls, 61 ± 13 yrs	Symptomatic Chinese patients with HFpEF, vs. controls and patients with DD	2D echo including LA strain and dyssynchrony assessment	LAVi max larger, LA reservoir function reduced, and interatrial dyssynchrony greater in HFpEF vs. other groups	LA diastolic and systolic function reduced, inter/intra-atrial dyssynchrony increased in HFpEF Interatrial dyssynchrony and reduced LA systolic strain associated with worse NYHA functional class Atrial dyssynchrony and reduced LA diastolic and systolic function contribute to HFpEF pathophysiology
Sanchis et al., 2015 (78) N = 138, 75 ± 9 yrs	Outpatients with new onset of HF symptoms	2D echo including LA strain analysis	LA systolic strain rate/LA volume ratio is a powerful diagnostic tool for defining symptomatic HF patients (AUC = 0.90)	LA dysfunction and HFPEF, suggest that the analysis of LA function may be useful in patients with new-onset dyspnea
Freed et al., 2016 (83) N = 308, 65 ± 13 yrs	Longitudinal follow-up of HFpEF patients with initial echo	2D, Doppler, and speckle-tracking echo and LA strain	LA reservoir strain strongest correlate of adverse events; associated with the composite outcome of hospitalization or death (adjusted HR per 1-SD decrease in LA strain: 1.54; 95% CI: 1.15–2.07; p = 0.006)	Abnormal indices of LA mechanics (particularly LA reservoir strain) are powerful clinical and prognostic factors in HFpEF
Santos et al., 2016 (84) N = 357, 69 ± 10 yrs	HFpEF patients enrolled in the TOPCAT trial	2D, Doppler, and speckle-tracking echo and LA strain	Lower peak LA strain associated increased risk of the composite endpoint (HR: 0.96 per unit of reduction in strain; 95% CI: 0.94–0.99; p = 0.009) and of HF hospitalization (HR: 0.95 per unit of reduction in strain; 95% CI: 0.92–0.98; p = 0.003)	LA dysfunction in HFpEF is associated with a higher risk of HF hospitalization independent of potential clinical confounders, but not independent of LV strain and filling pressure
Melenovsky et al., 2015 (75) N = 198 (101 HFpEF), 71 ± 10 yrs	Description of the characteristics of patients with HFpEF and prognostic value	2D, Doppler echo with measure of LA emptying fraction and LA stiffness	Lower LA emptying fraction associated with increased pulmonary vascular resistance, RV dysfunction and mortality	LA reservoir function associated with death in HFpEF patients. This LA dysfunction is linked to worse LA compliance and hemodynamic abnormalities

NYHA = New York Heart Association; TOPCAT = Treatment Of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist; other abbreviations as in Tables 2 to 4.

were reported after successful cardiac resynchronization therapy, probably due to improved diastolic filling (62), this experience has not been uniform (61).

Additionally, there is a complex interplay between the LA and LVDD, varying among different populations and clinical settings. In a population-based study of 2,042 subjects, the indexed LAV increased with worsening LVDD (63). Both indexed LAV and LVDD were predictive of all-cause mortality. However, when controlling for LVDD, indexed LAV was no longer an independent predictor of outcome (63). Thus, although LVDD contributes to LA remodeling, the latter seems to be only a biomarker of the clinical condition (LVDD) that is the actual determinant of patients' prognosis. On the other hand, in a recent study of 419 patients with a first myocardial infarction, significant (i.e., grade 2 or 3) LVDD emerged as an independent predictor of clinical outcomes (death, myocardial infarction, HF) (64). However, among the 4 individual parameters included in the LVDD diagnostic algorithm, only the indexed LAV was an independent predictor of adverse outcomes, although LAV alone was less powerful than the multiparametric algorithm (64). Thus, it remains difficult to determine the specific role of LVDD versus LA enlargement in different patient groups, and perhaps a combination of these 2 prognostic markers may provide additive value for determining adverse outcomes.

The LA dilatation caused by LVDD can in turn lead to AF (65), which is closely associated with LVDD and is very prevalent in patients with HFpEF. A recent review has comprehensively evaluated the role of LA metrics in AF (66). LA size is an unreliable parameter of LVDD and LV filling pressure in patients with AF. However, alterations in LA shape might better reflect altered LV diastolic function in the setting of AF. In a study of 104 patients referred for AF ablation, LA shape was evaluated by computed tomography, while LVDD was determined by echocardiography (67). LVDD and LAV were independently associated with LA asymmetry, whereas AF recurrence was associated only with asymmetric LA changes (67).

LA FUNCTION AND LVDD. With alterations in LV relaxation, the relative contribution of LA booster pump function to LV filling increases, whereas the

conduit function decreases. When LV filling pressures increase significantly, the limits of LA preload reserve are reached, and the LA will behave predominantly as a conduit.

Many studies have suggested that LA functional measurements may be superior to LA size in LVDD, even in the absence of LA dilatation. The use of LA strain as a functional adaptive marker has been demonstrated using TDI-derived strain to be a more sensitive measure of LVDD in apparently healthy individuals, with changes in LA strain preceding alterations in volumetric parameters by almost a decade (68). However, given that TDI strain is cumbersome and time consuming, speckle-tracking echocardiography-derived LA strain is now increasingly used.

In a multicenter study of 329 apparently healthy subjects, normal LA reservoir strain was 45.5 ± 11.4% with the lowest cutoff value being defined at 23% (69). These findings were validated by applying the derived cutoff for LA reservoir strain in 377 patients with LVDD, which demonstrated that LA strain was reduced in 23% of patients with a normal indexed LAV and in 27% with normal LA emptying fraction. Similar findings were reported in patients with hypertension and/or diabetes with normal indexed LAV (35) and in asymptomatic stage 3 chronic kidney disease patients (70), confirming its use and improved sensitivity as compared with LAV. More recently, in the cross-sectional BEFRI (BErlin Female RIsk evaluation) trial of 473 women, phasic LA function was compared with LAV in both those with normal diastolic function, and those with grade 1 and grade 2 LVDD (71). Both LA reservoir and conduit function progressively decreased with increasing grades of LVDD, whereas contractile function augmented in grade 1 LVDD before being reduced in patients with grade 2 LVDD. Receiver-operating characteristic curve analysis demonstrated higher accuracy with LA reservoir and conduit function versus indexed LAV in grading LVDD.

LA strain demonstrated a linear decrease with increasing grades of LVDD in a recent retrospective study of 90 patients with varying grades of LVDD and preserved LVEF (3). The LA reservoir strain values were then applied prospectively to grade LVDD. Whereas guideline recommended parameters graded 8% of patients as indeterminate LVDD, the addition of LA strain was able to classify all patients as normal or abnormal LV diastolic function. Similar increased accuracy of LVDD classification was demonstrated in 517 patients with hypertension, diabetes, and coronary artery disease with preserved LV ejection fraction (4). LA strain was reduced in 62%, whereas LAV was enlarged only in 34% of the patients. The addition of LA strain improved the detection of LVDD by ~10%.

CLINICAL APPLICATIONS OF LA SIZE AND FUNCTION IN EVALUATION OF LVDD. LA strain is a sensitive marker particularly of early LVDD, and—unusually among diastolic variables—LA reservoir function decreases in a linear fashion as LVDD progresses (**Central Illustration**). This would suggest that LA strain could be incorporated into routine evaluation of LVDD, at least specifically in patients who are classified in the indeterminate LVDD group, using the recommended algorithm (2). **Table 3** summarizes the studies of LA structural and functional alterations in patients with LVDD.

LA functional reverse remodeling appears to occur despite lack of structural improvement (i.e., decrease of LAV). The effects of changing LV filling pressures on LA structure and function were investigated with sequential echocardiograms in 195 patients in sinus rhythm with LA dilatation at baseline. Although the decrease in LAV with reduction in LV filling pressures was limited, and normalization of the dilated LA was rare, the changes in LV filling pressure were associated with recovery, and normalization in LA strain was independent of changes in LAV (61).

DYNAMIC CHANGES IN LVDD: EVALUATION WITH EXERCISE. The most common presenting symptom of LVDD is dyspnea on exertion. Hence, evaluation of cardiac function parameters during exercise is important, providing additional diagnostic value for determining the presence and severity of LVDD. An increase in late diastolic mitral annular velocity (a′ velocity, a measure of LA contractile function) during exercise was demonstrated in normal subjects and asymptomatic hypertensive patients, but not in patients with HFpEF. Asymptomatic hypertensive patients could compensate for the increase in LV filling pressure during exercise by increasing LA contractile function, whereas patients with HFpEF were unable to do so (72). This suggests some plasticity in LA function early in the course of LVDD that is lost once LV filling pressures are chronically elevated.

The importance of LA function as a physiological marker is further emphasized by its association with exercise capacity. In a study of 486 patients with preserved LV ejection fraction, resting LA strain was positively associated with exercise capacity, with a strength of association similar to that of elevated E/e′ (73) (**Table 4**).

Thus, the role of LA function for the evaluation of LVDD is promising, although some technical

challenges still need to be overcome. LA function assessment could provide important information in the setting of indeterminate LVDD, and evaluation during exercise may help unmask LV diastolic function abnormalities in patients with normal function in the resting state.

HF WITH PRESERVED EJECTION FRACTION

About 40% to 50% of the patients presenting with the clinical syndrome of HF have HFpEF, and this percentage is growing. Both morbidity and mortality in HFpEF are similar to those in HFrEF (57), and noncardiovascular comorbidities have a significant impact on prognosis in HFpEF patients (74). Although there is currently no established treatment for HFpEF, what is even more problematic is the lack of a specific diagnostic algorithm for this syndrome. Moreover, the pathophysiological mechanisms underlying HFpEF remain unclear. We know that despite preserved LVEF, these patients are more likely to have LV hypertrophy or concentric remodeling, LVDD, and LA enlargement (13). However, what is unclear is when the transition from LVDD to HFpEF occurs, and whether this may be precipitated by alterations in LA function.

LA SIZE IN EVALUATION OF HFpEF. Clearly, the LA is important, both to make the diagnosis and perhaps to assess the prognosis in patients with HFpEF. A recent consensus statement includes indexed LAV (>34 ml/m^2), an estimate of LA pressure (E/e′ ≥13), together with parameters of LV systolic (LV ejection fraction) and diastolic function, to make the diagnosis of HFpEF (57) (**Figure 6**). The increase in maximum LAV in HFpEF is smaller than in HFrEF despite similar LA pressures, suggesting a different pathophysiology, with HFpEF more associated with increased LA stiffness (75). Moreover, LA size has been demonstrated to be independently associated with increased morbidity and mortality in HFpEF (76). In a multicenter study of patients with an acute HF admission, indexed LAV, and tricuspid regurgitation velocity >2.9 m/s were determinants of HF-related hospitalizations and death (76). In a relatively small cohort of HFpEF patients, indexed minimum LAV had the strongest association with HF hospitalizations on multivariable analysis (77).

LA FUNCTION IN THE EVALUATION OF HFpEF. Although LAV can be accurately measured by either 2DE or 3DE, the most promising parameter in HFpEF seems to be those related to LA function assessed by speckle-tracking echocardiography (78). LA reservoir function is the main parameter that has been studied (79). LA conduit and booster pump function may also have value, and both are impaired in HFpEF patients (80). LA contractile function had diagnostic use in a group of patients with suspected HF with an area under the receiver-operating characteristic curve of 0.8 to identify HF patients (78). LA conduit strain also correlated with early diastolic filling volume. Increased inter-atrial/intra-atrial dyssynchrony was also noted in HFpEF patients, with reduced LA strain, and was positively correlated with increased New York Heart Association functional class (81).

The cardinal clinical manifestation of HFpEF is exertional dyspnea. Abnormal LA strain (i.e., LA reservoir strain <23%) was associated with worse New York Heart Association functional class and elevated estimated pulmonary capillary wedge pressure, even when LAV was normal (4). Thus, LA strain abnormalities at rest could be an important biomarker of HFpEF even in the absence of LA enlargement. However, the response to provocative maneuvers, such as the lack of change in LA reservoir strain with leg lifts (i.e., increase in LA preload) in patients with HFpEF as compared with hypertensive patients (37), may significantly improve diagnostic accuracy, especially in patients with normal LA strain at rest. The value of exercise testing was highlighted in a small group of HFpEF patients by demonstrating that even in subjects with normal LAV and LA reservoir strain at rest, exercise could unmask a failure of augmentation of LA strain and strain rate in HFpEF patients (82).

Moreover, LA reservoir strain is also a promising prognostic marker in HFpEF. In 135 HFpEF patients involved in a substudy of the PARAMOUNT (Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion) trial, the lower absolute reservoir LA strain was associated with previous hospitalization and history of AF (80). Moreover, lower absolute LA strain was associated with significantly lower LV strain and higher LV mass. In 308 HFpEF patients followed longitudinally for ~3 years, among LV, right ventricular, and LA strain measures, LA reservoir strain was the parameter with the stronger association with adverse cardiovascular outcomes (83). Additionally, LA reservoir strain correlated with pulmonary vascular resistance and peak oxygen consumption, emphasizing the pathophysiological heterogeneity in HFpEF, in addition to the association with altered LV compliance. These findings, however, need to be validated in larger patient cohorts.

Evaluation of the importance of LA dysfunction to predict the composite endpoint of cardiovascular death, HF hospitalization, and aborted sudden death was explored in 357 HFpEF patients enrolled in TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial) (84), among whom 52% of patients had abnormal LA reservoir strain. LA reservoir strain was more impaired in patients with LA geometry abnormalities: LA reservoir strain was abnormal in 47% of the patients with normal LA size and in 71% of patients with LA enlargement. Reduced LA reservoir strain was associated with a higher risk of HF hospitalization, but not after adjusting for LV global longitudinal strain and filling pressure (84) (**Table 5**). These data again demonstrate the close interplay between LV and LA function based on varying populations and specific clinical settings, and suggest again that an algorithm using both LA and LV function parameters should be used in the diagnosis and to stratify prognosis in HFpEF, similar to LVDD. Given the large variability of results, both the prognostic use of LA reservoir strain in HFpEF and its independent incremental value over LV characteristics need validation in larger patient cohorts before it can be implemented in the clinical routine.

CLINICAL APPLICATIONS OF LA SIZE AND FUNCTION IN EVALUATION OF HFpEF. LA enlargement and elevated LA pressures are cardinal features to reach the diagnosis of HFpEF; recent evidence demonstrates the additive use of LA strain for diagnosis of HFpEF as well (77). However, LA geometry and function should not just be limited to make the diagnosis and stratify prognosis in patients with suspected or confirmed HFpEF, but they should also be therapeutic targets (i.e., as a target for therapy and also to determine the effectiveness of therapy). Unloading the LA and improving its function may be important therapeutic endpoints in HFpEF. Responsiveness of LA strain parameters to drug- and/or device-based treatments to unload the LA may be an important future surrogate endpoint to determine effectiveness of therapy. There is recent evidence that creation of a small atrial septal defect, which results in a pressure-dependent unidirectional left-to-right atrial shunt, may protect against the negative hemodynamic impact of LA hypertension and prevent acute cardiac decompensation (85). Quantifying LA function by LA strain may be a useful therapeutic target, providing useful information on the adequacy and benefits of such interventions, but caution needs to be applied in relation to possible confounding effects by other independent atrial pathology (e.g., prior AF).

CURRENT KNOWLEDGE GAPS

Assessment of LA phasic function is a new concept that may improve the accuracy of the diagnosis and prognostic stratification of both LVDD and HFpEF, and perhaps may be useful to monitor treatment response in HFpEF patients. Whereas maximum LAV has been extensively evaluated, the clinical use of minimum LAV and phasic LAV changes are less well-documented, as are the reference values of LA phasic function. The utility of 3DE LAV and their reference values need to be confirmed in larger patient groups.

The methodology to obtain LA strain measurements requires standardization. The practical application of the indications included in the recent consensus document provided by EACVI/ASE/Industry Task Force about strain standardization (36) needs to be tested in various patient cohorts and across the different echocardiography platforms.

Because assessment of LA stiffness will be potentially important in characterizing patients with suspected LVDD, and particularly in differentiating patients with HFpEF from those with LVDD without HF, speckle-tracking-derived LA longitudinal strain should be tested against TDI-derived LA longitudinal strain to derive an LA stiffness index.

Finally, more work is required to define when reverse LA remodeling will be unlikely to occur. Combining LA function with volume, and their changes from resting conditions to exercise will undoubtedly enhance the diagnostic and prognostic potential of LA geometry and function in LVDD and HFpEF, whereas the value of LA shape and LA wall composition have still to be investigated.

CONCLUSIONS

The LA has varying roles throughout the different phases of the cardiac cycle, with strong LA-LV interactions through all the phases. Measurement of LA function metrics may improve the diagnostic accuracy and prognostic value of both diastolic dysfunction and HFpEF algorithms. Measurement should be performed, not only in the resting state, but also during provocative maneuvers (leg lifts or exercise), as well. The availability of LA strain has provided a feasible biomarker of LA function, which should be considered in routine practice.

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