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REVIEW ARTICLE

Evaluation of Left Atrial Function: Current Status

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ABSTRACT

This review examines the current status of measuring left atrial mechanical functions and the ability of atrial functional analysis to predict cardiovascular outcomes. Increasing data support the use of echocardiography, computed tomography, and cardiac magnetic resonance in this regard. This review will discuss the various techniques used to assess left atrium reservoir, conduit, and booster pump functions and will focus on their ability to predict cardiovascular events in general and referral populations, and in patients with atrial fibrillation and other heart diseases.

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KEYWORDS Cardiac computed tomography; cardiac magnetic resonance; cardiovascular outcomes; echocardiography; left atrial function; tissue tracking

Introduction

The principal mechanical role of the left atrium (LA) is to modulate left ventricular filling and cardiovascular performance; this is accomplished by its distinct, but inter-related functions as a *reservoir* for pulmonary venous return during ventricular systole, as a *conduit* for pulmonary venous return during early ventricular diastole, and as a *booster pump* that augments ventricular filling during late ventricular diastole. Importantly, there is considerable interplay between these atrial functions and ventricular performance throughout the cardiac cycle. Thus, while reservoir function is most rigorously defined by the atrial pressure-volume relation during ventricular systole, it is influenced by descent of the LV base during systole, left ventricular end-systolic volume, and atrial contractility and relaxation.[1] Conduit function is influenced by atrial compliance during ventricular diastole, but by necessity (as the mitral valve is open) is closely related to LV relaxation and compliance. Finally, atrial booster pump function reflects the magnitude and timing of atrial contractility, but is dependent on the degree of venous return (atrial preload), left ventricular end diastolic pressures (atrial afterload), and left ventricular systolic reserve. These relationships need to be considered when evaluating the various atrial functions.

Atrial function can be assessed with echocardiography, cardiac computed tomography (CCT), and cardiac magnetic resonance (CMR or MRI). Arguably, echocardiography is best suited for this charge because of its availability, safety, versatility, and ability to image in real-time with high temporal and spatial resolution; however, CCT and especially CMR have important and complimentary roles in specific clinical instances[2] (Table 1).

While maximum LA volume indexed for body surface area (LAVi) strongly associates with cardiovascular disease, predicts cardiovascular outcomes, and provides uniform and accurate risk stratification,[3] an increasing body of data suggests that left atrial function provides incremental prognostic information that is more powerful and occurs earlier in disease processes than does an increase in LA size.[4,5] The different methods for measurement of LA function and the increasingly recognized ability of these methods to determine prognosis and risk stratification is the focus of this review. Other roles related to the release and action of atrial natriuretic peptide and the regulation of mechanoreceptors at the veno-atrial junctions, which play a critical role in the homeostatic control of water and electrolytes, will not be discussed in this examination of atrial function.

Discussion

Assessing left atrial functions

Most often, LA function is assessed echocardiographically using volumetric analysis, spectral Doppler of transmitral, pulmonary venous, and left atrial appendage flows, and tissue Doppler and deformation analysis (strain and strain rate imaging) of the left atrial body (Table 2, Figure 1). Both CCT and CMR have been used to assess volumetric left atrial functions,[6–9] and CMR strain and strain rates can be determined using tagged sequences and more recently using feature tracking (FT). Late gadolinium enhancement can quantify scar, which is inversely related to impaired reservoir function and has been useful in predicting the risk of atrial fibrillation (AF) recurrence after LA ablation.[10] CCT is used infrequently for volumetric analysis of LA function, but plays an important role in the pre-, intra- and post-procedural stages of LA ablation.

An alternative, time-independent representation of the atrial events during the cardiac cycle can be obtained by plotting instantaneous atrial pressure and volume (Figure 2a). During

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Table 1. Relative strengths, weaknesses, and uses of TTE, CMR, and CCT.

	TTE	CMR	CCT
Availability	+++	+	++
Typical study duration (min)	30	30–50	10
Cost	Low	High	Moderate
Safety	+++	+	++
Spatial resolution	+	++	+++
Temporal resolution	+++	++	+
Anatomic detail	+	++	+++
Tissue characterization	+	+++	++
Static LA volumes	+	+++	++
Phasic LA volumes	+++	++	+
LA mechanics	+++	++	
Primary uses	First-line evaluation and follow-up	Evaluation if poor echo windows Pre- and post RFA if concerns about radiation, contrast Pre- and post RFA atrial scar	Pre- and post RFA Epicardial fat analysis

Note. TTE, transthoracic echocardiography; CMR, cardiac magnetic resonance; CCT, cardiac computed tomography; +++, best; ++, intermediate; +, worst; RFA, radiofrequency ablation. Adapted from Ref. 2.

Table 2. Volumetric, Doppler, and deformational indices of left atrial function.

Volumetric indices			
LA function	LA volume fraction	Calculation	
Global function; reservoir	LA EF (or total EF)	[(LAmax-LAmin)/LAmax]	
Reservoir function	Expansion index	[(LAmax-LAmin)/LAmin]	
Conduit[a]	Passive EF	[(LAmax-LApre-A)/LAmax]	
Booster pump	Active EF	[(LApre-A-LAmin)/LApre-A]	
Spectral Doppler indices			
LA function	Transmitral flow	Pulmonary venous flow	Composite indices
Global function			LAFI
Reservoir		S vel	
Conduit	E vel, E/A	D vel	
Booster pump	A vel, E/A, AFF	PVa	Ejection force, LAKE
Tissue Doppler and Deformational indices			
LA function	Tissue velocity	Strain	Strain rate
Reservoir	S′	εs, εtotal	SR-S
Conduit	E′	εe, εpos	SR-E
Booster pump	A′	εa, εneg	SR-A

Note. [a]Conduit volume is actually the volume of blood that blood that passes through the LA that cannot be accounted for by reservoir or booster pump functions: [LV stroke volume – (LAmax-LA min)].

EF, ejection (or emptying) fraction; LAmax, maximal LA volume; LAmin, minimal LA volume; LApre-A, LA volume immediately before atrial systole; LAFI, LA functional index; S and D refer to ventricular systole and diastole; E and A (caps and lower case) refer to early and late diastole; vel, velocity; AFF, atrial filling fraction; LAKE, LA kinetic energy; PVa, pulmonary venous reversal velocity; +, strain; pos, positive; neg, negative; SR, strain rate.

ventricular systole, atrial relaxation and descent of the ventricular base lowers atrial pressure and assists in atrial filling; thus, during ventricular systole, the LA operates as a reservoir, storing pulmonary venous return. When the mitral valve opens, blood stored in the LA empties into the LV and atrial pressure falls, during which time the atria act as conduits for venous blood flow. Subsequently, atrial contraction actively assists ventricular filling. The resultant P-V loop inscribes a figure-eight that consists of a clockwise "V" loop due to atrial filling and passive emptying and a counterclockwise "A" loop due to active atrial contraction. Atrial elastance, (analogous to ventricular elastance) can be used to derive relatively load-independent measures of atrial contractility (Figure 2b), and by fitting atrial pressures and volumes from the ascending limb of the "V" loop, one can obtain rigorous measurements of LA compliance, an important component of reservoir function. While atrial pressure-volume loops can be generated in humans using invasive and semi-invasive means,[11] these methods are cumbersome, time consuming and difficult to apply clinically.

Echocardiographic methods

Volumetric methods

Quantifying LA size is difficult, in part because of the complex geometry and fiber orientation of the LA, and the variable contributions of its appendage and pulmonary veins. LA volume calculated from two orthogonal apical views using the area-length (described below) or method of disc technique is superior to and predicts cardiovascular outcomes more powerfully than M-mode dimensions and 2D areas, and have been validated against several reference standards.[3] LA volume is computed as 0.85 ($A_{4\text{-chamber}} \times A_{2\text{-Chamber}}$)/L, where A is LA area and L is the shorter of the two long axes, measured as the distance from the midpoint of the mitral annular plane to the roof of the LA. Care

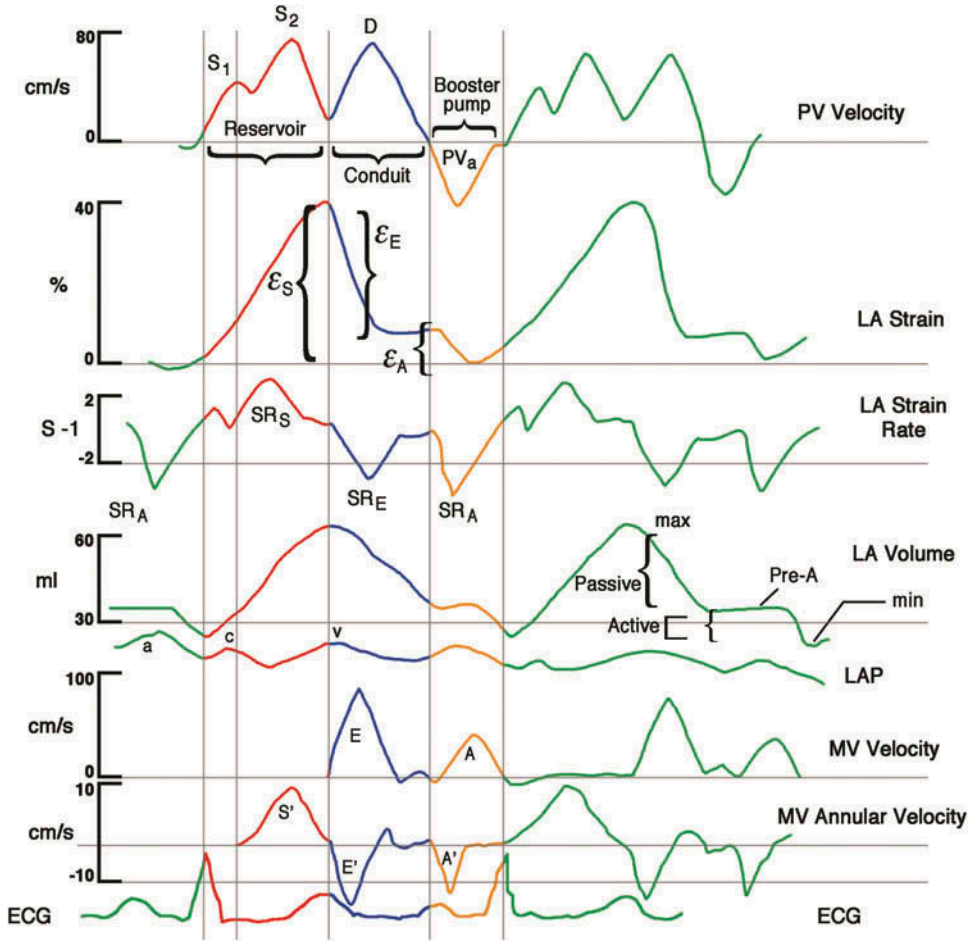

Figure 1. Functions of the left atrium and their color-coded relation to the cardiac cycle (red, reservoir; blue, conduit; yellow, booster pump). Displayed are pulmonary venous (PV) velocity, LA strain, LA strain rate, LA volume and pressure, and mitral spectral and tissue Doppler. Abbreviations as in Table 1 and text. (Reproduced from B. D. Hoit, Left Atrial Size and Function Role in Prognosis, *Journal of the American College of Cardiology*, 63(3):493–505, © 2014, with permission from Elsevier. Permission to reuse must be obtained from the rightsholder.)

must be taken not to foreshorten the long axis of the LA, which may be suspected if the two long axes are greater than 5 mm. Inaccuracies owing to geometric assumptions and foreshortening of the LA cavity with 2D biplane volume methods are overcome with real time 3D echo (RT3DE) (Figure 3), which has been shown to accurately and reproducibly estimate LA volume when compared to CMR.[12] RT3DE LA volumes are measured either using vendor-dependent software designed for LV volumes or dedicated vendor-independent software based on semiautomated detection of LA boundaries.[12] RT3DE LA volumes are superior to 2D volumes for longitudinal follow-up and serial measurements,[13] but are time-consuming, and require high 2D image quality and the need to "stitch" subvolumes, which may be particularly problematic in AF; moreover, algorithms are vendor-dependent and there is a relative paucity of normative values. Accordingly, echo guidelines call for LA volume determination using 2D biplane area-length or method of discs.[14]

A volumetric assessment of LA reservoir, conduit and booster pump functions can be obtained from LA volumes at their maximal (at ventricular end-systole, just before mitral valve opening), minimum (at ventricular end-diastole, when the mitral valve closes), and immediately before atrial systole (prior to the electrocardiographic P wave). From these volumes, total, passive and active emptying fractions (measures of reservoir, conduit, and booster pump function) and the expansion index (a measure of reservoir function) can be calculated (Table 2).

Echocardiographic LAVi and total LA emptying fraction were shown to be powerful predictors of new onset AF and flutter after adjustment for baseline clinical risk factors, LV ejection fraction, LV diastolic functional grade and LA volume in 574 elderly participants referred for an echocardiogram and followed prospectively for a mean of 1.9 years. Patients at highest risk were those with both LA total emptying fraction ≤ 49% and LAVi ≥ 38 ml/m^2,[15] LA emptying fraction was superior and incremental to LAV suggesting that reservoir function of the LA represents a more advanced state of left atrial remodeling than LA enlargement alone.

A novel measure of atrial function, the LA functional index (LAFI), is the product of LA emptying fraction and LV outflow tract velocity time integral, divided by the LAVi. The LAFI was studied in 855 patients with coronary artery disease and an LV EF ≥ 50% that were followed for a median of 7.9 years as part of the Heart and Soul Study. Each standard deviation decrease in LAFI was associated with a 2.6-fold increase in the hazard of adverse cardiovascular events.[16] In another study of 72 patients with chronic AF

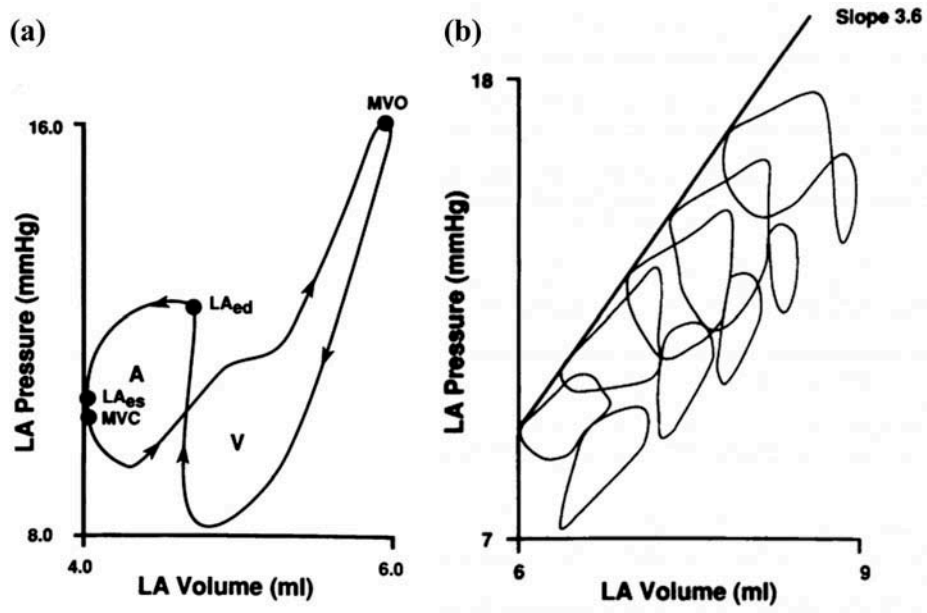

Figure 2. (A) LA pressure-volume loop from a single beat illustrating the characteristic figure-of-eight configuration Arrows indicate the direction of the loop as a function of time. The "A" loop represents active atrial contraction. The "V" loop represents passive filling and emptying of the left atrium. Compliance of the left atrium is measured by fitting atrial pressures and volumes from the ascending limb of the "V" loop. MVO, time of mitral valve opening; LAed, left atrial end-diastole; LAes, left atrial end-systole. (B) Computer-smoothed pressure-volume loops generated by preload alteration. Note the linearity of the end-systolic pressure-volume relation, the slope of which is end-systolic elastance, a load-independent index of atrial contractility. (Reproduced from B. D. Hoit et al., In vivo assessment of left atrial contractile performance in normal and pathological conditions using a time-varying elastance model, *Circulation*, 89(4), © 1994, with permission from Wolters Kluwer Health, Inc. Permission to reuse must be obtained from the rightsholder.)

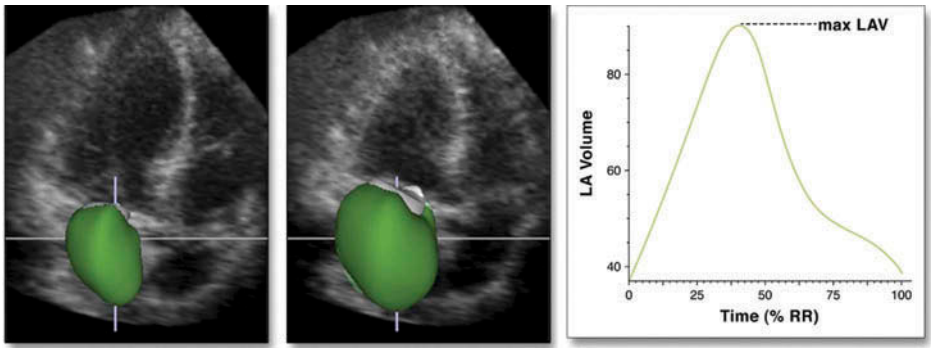

Figure 3. 3D rendered minimum (left panel) and maximum LA volumes (center panel) and the volume-time curve (right panel) that allows accurate measurement of total, passive, and active stroke volumes and calculation of total, passive, and active ejection fractions. (Reproduced from A.C. To et al., Clinical Utility of Multimodality LA Imaging Assessment of Size, Function, and Structure, *JACC: Cardiovascular Imaging*, 4(7):788–798, © 2011, with permission from Elsevier. Permission to reuse must be obtained from the rightsholder.)

undergoing cardioversion and followed for 6 months, the LAFI was significantly depressed in those that remained in persistent AF compared to those in whom sinus rhythm was restored, and progressively improved in patients remaining in sinus rhythm.[17]

Although assessment of LA function using volumetry is used frequently in research laboratories, acquisition and analysis are time consuming and reproducibility is modest; accordingly functional LA measures from volumetry are not included in guideline documents and are not routinely used clinically. However, myocardial tracking allows one to quickly generate LA volume time-curves from which maximum, minimum, and pre-A volumes can be derived and their fractional volumes calculated.[18] STE volume-time curves are closely correlated with 2D-determined volumes and can be obtained in half of the time with greater reproducibility.[18]

Spectral Doppler

Doppler waveforms of pulmonary venous and transmitral flow, which represent left atrial filling and emptying respectively, can be used to estimate *relative* atrial functions. Advantages are their availability and simplicity in acquisition and interpretation. The ratios of peak transmitral early (E) and late (A) velocities (or their velocity-time integrals, vti) and the atrial filling fraction (Avti/[Evti +Avti]) estimate the relative contribution of atrial booster pump function, and the ratio of systolic (S) to diastolic (D) pulmonary venous flow estimate relative reservoir to conduit function. The magnitude and duration of reversed pulmonary flow (PVa) during

atrial contraction is used to estimate atrial contractility and LV diastolic pressures.[19] Low left atrial appendage velocities (usually obtained from transesophageal echo) reflect reduced appendage contractile function and predict the risk of thromboembolism and maintenance of sinus rhythm after cardioversion.[20,21] Several studies suggest that reduced atrial booster pump function identifies cardiovascular risk in the general population.[22,23] A low transmitral Doppler atrial filling fraction (and increased E/A vti) predicted new onset AF in 942 subjects of the Framingham Study independent of left atrial size; in that study, a one standard deviation decrease in the atrial filling fraction was associated with a 28% higher risk of AF, suggesting that decreased booster pump function predates atrial arrhythmia.[22]

Atrial ejection force and LA kinetic energy (LAKE) are combinatorial indices of atrial systolic (booster pump) function. LA ejection force ($0.5 \times \rho \times$ mitral valve orifice area $\times A^2$, where ρ is the density of blood) is the force exerted by the left atrium to accelerate blood into the LV[28] and LAKE ($0.5 \times$ LA active stroke volume $\times \rho \times A$) is a measure of atrial work.[24] In 2808 unselected participants in the Strong Heart Study having a high prevalence of obesity and diabetes but without prevalent cardiovascular disease, reduced LA ejection force was associated with a higher rate of combined fatal and nonfatal cardiovascular events, independent of age, risk factors, LV geometry and diastolic functional grade.[23] In another study, left atrial work estimated by LAKE was independently predictive of cardiovascular death and hospitalization for CHF in 243 heart failure patients followed for a median of 3.1 years; perhaps because it is incorporated in the formulation of LAKE, maximal LAV did not independently predict cardiovascular events.[25]

Despite their advantages, interpretation of spectral Doppler indices can be difficult in patients with sinus tachycardia, conduction system disease, and arrhythmia (especially AF), and obtaining high-quality pulmonary venous recordings may be difficult. A major disadvantage of spectral Doppler is its non-specificity, since changes may be due to LV diastolic dysfunction, mitral valve disease, or abnormal hemodynamics. Finally, despite their sound foundation on physical principles, there have been no clinically useful applications for either LA force or kinetic energy and they have been used sparingly in the research arena.

Tissue Doppler

Pulsed wave and color tissue Doppler of atrial contraction (A') provide a regional and by averaging several sites, a global snapshot of atrial systolic function.[26,27] Reproducible data with acceptable variability is achievable with proper attention to technical details. Off-line color tissue Doppler waveforms record simultaneously multiple atrial regions and demonstrate a decremental gradient of atrial contraction from annular to superior segments.[27] Tissue velocities during ventricular systole (S') and early diastole (E') correspond to reservoir and conduit function, respectively, but have not been shown to have clinical value.

In contrast, tissue Doppler annular velocity after atrial contraction (A') was a significant independent predictor of cardiac mortality in 518 subjects (353 of whom had cardiac diseases) after 2 years; when A' was ≤ 4 cm/s, the hazard ratio of cardiac death was significantly greater than when it was > 7 cm/s.[28]

Tissue Doppler velocities are not without their limitations. They are subject to error because of angle dependency and the effects of cardiac motion and tethering, and as a result, they have been superseded by strain and strain rate imaging.

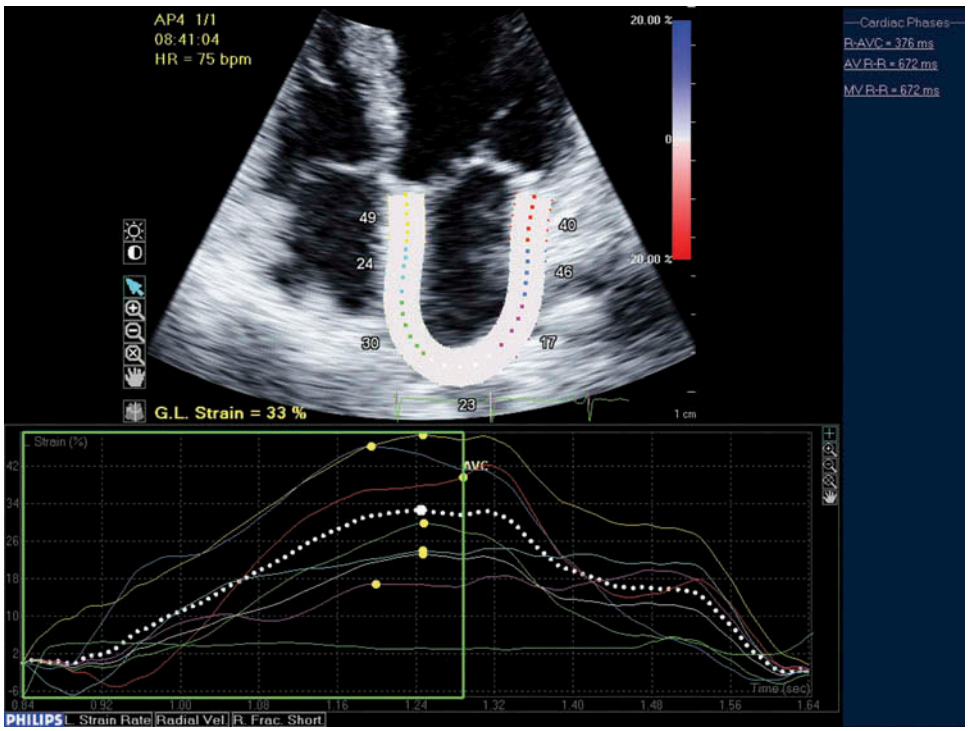

Figure 4. Example of speckle tracking echo-derived LA strain. Regional strains are denoted by the colored lines, global longitudinal (GL) strain by the white dotted line. The closed circles on each regional strain-time curve identify peak strain. AVC, aortic valve closure. (Reproduced from B. D. Hoit, Left Atrial Size and Function Role in Prognosis, *Journal of the American College of Cardiology*, 63(3):493–505, © 2014, with permission from Elsevier. Permission to reuse must be obtained from the rightsholder.)

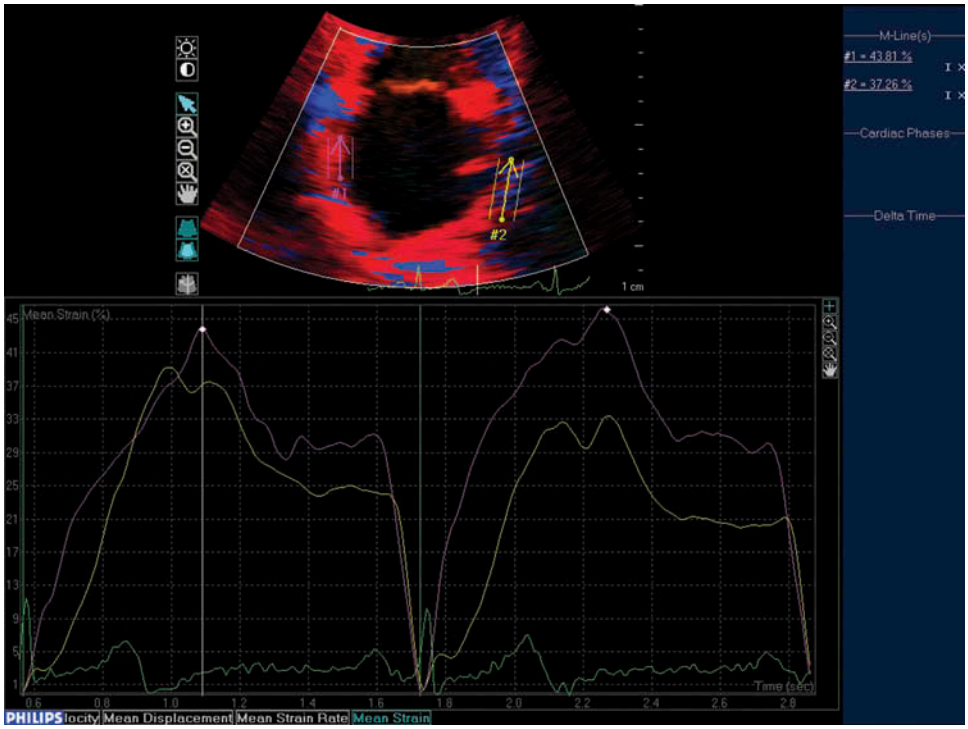

Figure 5. Example of tissue-Doppler imaging LA strain. Strain curves for the inferior (purple) and anterior segments (yellow) are shown. (Reproduced from B. D. Hoit, Left Atrial Size and Function Role in Prognosis, *Journal of the American College of Cardiology*, 63(3):493–505, © 2014, with permission from Elsevier. Permission to reuse must be obtained from the rightsholder.)

Strain and strain rate imaging (deformation analysis)

Strain and strain rates represent the magnitude and rate, respectively, of myocardial deformation (for a review see Ref. 29); they can be measured using either color tissue Doppler velocities (Tissue Doppler Imaging, TDI) or by 2D echocardiographic (2D speckle-tracking or STE) techniques (Figures 4 and 5). Deformation analysis has been used successfully to determine left atrial global and regional functions[30,31] and assessment of LA function has been useful to predict the success of restoring sinus rhythm in patients with AF following either DC cardioversion or AF ablation;[32–34] predict reverse atrial remodeling (defined as a ≥ 15% reduction in maximal LAV) in patients undergoing ablation for AF;[35] predict outcomes in patients with coronary artery disease;[36–38] predict exercise capacity in heart failure;[39,40] and predict the development of AF in valvular heart disease.[41,42] LA strain can also be used to estimate LV filling pressures non-invasively. A global peak atrial longitudinal strain < 18% had greater diagnostic accuracy to detect LV end diastolic pressure (LVEDP) > 12 mmHg than did E/E,' irrespective of the LV EF.[43] Moreover, LA systolic strain was significantly lower in patients with heart failure with preserved ejection fraction (HFpEF) than in patients who had LV diastolic dysfunction without heart failure, and among the variables LV volume and mass, and LA volumes, emptying fraction and systolic and contractile strains, the LA stiffness index, the ratio of PCWP or E/E' to LA systolic strain, was the most accurate means of distinguishing patients with heart failure from those with isolated diastolic dysfunction.[44]

Using instantaneous tissue Doppler velocities, one can mathematically estimate strain rate (SR) by measuring the spatial velocity gradient, SR ≈ $(V_2 - V_1)/d$, where V_2 and V_1 are instantaneous velocities measured at points 2 and 1, respectively, and d is the distance between the two points; myocardial strain is then derived by integrating the Doppler-derived strain rates. Although temporal resolution with TDI is excellent and optimal 2D image quality is not necessary, TDI is highly angle-dependent and signal to noise may be problematic. In contrast, 2D STE analyzes myocardial motion by frame-by-frame tracking of natural acoustic markers that are generated from interactions between ultrasound and myocardial tissue within a user-defined region of interest, without significant angle dependency. However, frame rates of ~50–70 are needed to avoid speckle decorrelation and good image quality is needed for accurate tracking. For both modalities, strain imaging of the left atrium is more difficult and time-consuming than it is for the left ventricle. The far-field location of the atrium and reduced signal to noise (image resolution and tracking ability are better in the proximal part of the sector), the thin atrial wall, and the presence of the appendage, atrial septal abnormalities, and pulmonary veins are challenges for applying deformation analysis to the left atrium. Moreover, there is a lack of consensus regarding the number of traced LA views (i.e., four-chamber, biplane, triplane) and which regions to include in calculating global strains; of interest, the European task force recommends LA STE be performed only in the lateral wall.[45] Whether peak global systolic strain is superior to GLS of the LV, which reflects in part atrial reservoir function, also remains unsettled.[38]

Regional strains have not been as rigorously studied as global strains, but may be useful to identify LA dyssynchrony, which may reflect a heterogeneous pattern of LA fibrosis and dysfunction.[46] Atrial dyssynchrony has been defined by both the maximal time to peak delay of opposing atrial walls[47] and as the mechanical dispersion (the standard deviation of

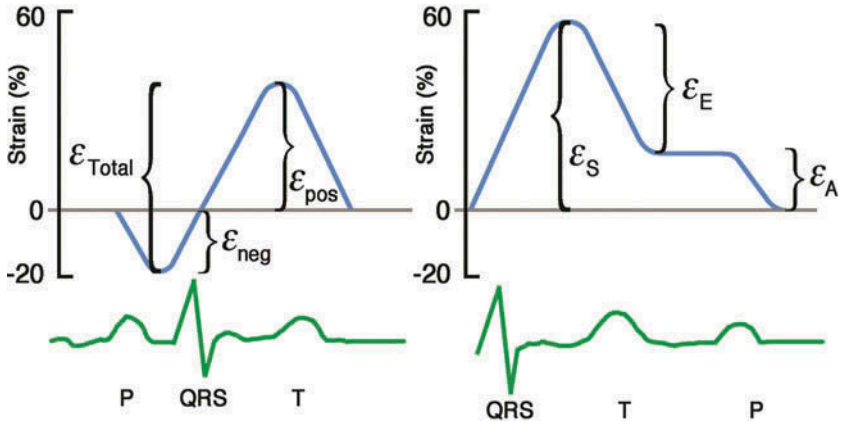

Figure 6. Strain nomenclature based on choice of zero reference point. The electrocardiographic P-wave is used on the left and the QRS complex on the right. Abbreviations as in Table 1 and text. (Reproduced from B. D. Hoit, Left Atrial Size and Function Role in Prognosis, *Journal of the American College of Cardiology*, 63 (3):493–505, © 2014, with permission from Elsevier. Permission to reuse must be obtained from the rightsholder.)

contraction durations defined as the time from the peak electrocardiographic P wave to maximal atrial systolic shortening in each segment),[48] which have been shown to "predict" AF recurrence after radiofrequency ablation.

It is important to recognize that differences in nomenclature used to describe atrial strain and strain rate are dependent on whether the atrial or ventricular cycle is used as the reference (i.e. zero baseline) point (Figure 6). If the ventricular cycle is used, ventricular end-diastole (the QRS complex) is the zero reference, and the peak positive longitudinal strain (εs) corresponds to atrial reservoir function and the strain during early and late diastole (εe and εa, respectively) correspond to conduit and atrial booster function. If the atrial cycle is used, atrial end-diastole (onset of P wave) is the zero reference, and the first negative peak strain (εneg) represents the atrial booster pump function, the positive peak strain (εpos) corresponds to conduit function, and their sum (εtotal) represents reservoir function.[49–51] Strain rates in ventricular systole, early diastole, and late diastole (respectively, SR-S, SR-E, and SR-A) correspond to reservoir, conduit and booster pump functions in both schemes. While there is not consensus, the European task force recommends that the zero reference be the P wave for patients in sinus rhythm and the QRS complex for those in AF,[45] a recommendation that acknowledges that the QRS reference is mandatory for AF and that in sinus rhythm, a P wave reference accurately reflects the direction of deformation. Although there are differences in normative values using these two approaches, it is not immediately clear why; unfortunately, the lack of standardization is likely to slow the implementation of this potentially valuable technique.

Normal reference ranges of reservoir, conduit and contractile strain were recently reported in a systematic review and meta-analysis of 40 studies (2542 patients)[52] (Table 3). Between-study heterogeneity was explained by heart rate, BSA, and sample size. The analysis did not show the expected age-related changes (i.e. decrease in reservoir and increase in contractile strain), most likely because patient-level data were not analyzed and the age range was relatively narrow. While racial and ethnic differences were not identified, the majority of studies were in Caucasians. Whether QRS or P wave gating were used didn't matter, but all but three studies used the QRS as the zero baseline. Similarly, since 85% of the studies were performed on the GE system, statements regarding vendor equivalence were not possible.[52]

While 2D strain and strain rate imaging overcomes much of the subjectivity and variability inherent in assessing endocardial motion, these methods fail to address the complexities of cardiac geometry and motion. Initial data suggest that three dimensional speckle tracking echo (3DSTE) overcomes these limitations as it eliminates the effects of through-plane motion that may occur with 2D imaging.[50,53] 3DSTE is a reproducible technique that more quickly and completely analyzes myocardial deformation; thus, one can measure longitudinal and circumferential strain from the same 3D data set and the LA endocardial area strain

Table 3. Reference ranges for 2D-STE and FT-CMR strain from selected studies.

2D STE			FT-CMR		
ε_s	ε_e	ε_a	ε_s	ε_e	ε_a
Pathan et al.[52]			Kowallick et al.[58]		
39% (38–41)	23% (21–25)	17% (16–19)	29% (5.3)	21% (5.1)	7.8% (2.5)
Median (IR)			Mean (SD)		
40 studies	14 studies	18 studies	n = 10		
Sun et al. (*Int J Cardiol*. 2013;168:3473)			Evin et al.[65]		
46.8% (7.7)	27.3% (6.4)	19.6% (4.2)	24.6% (6.4)	10.4% (4.4)	14.2% (6.5)
N = 121	QRS zero reference		N = 10 young healthy controls		
Saraiva et al.[48]			Evin et al.[65]		
35.6% (7.9)	21.4% (6.7)	14.2% (3.3)	22.6% (4.9)	8.7% (3.1)	14.0% (4.1)
N = 64	P wave zero reference		N = 10 elderly healthy controls		

Note. STE, speckle tracking echocardiography; FT-CMR, feature tracking cardiac magnetic resonance; $+_s$, systolic or reservoir strain; $+_e$, conduit or early diastolic strain; $+_a$, late diastolic or booster pump strain; IR, interquartile range; SD, standard deviation.

(εarea, longitudinal times circumferential strain) can be evaluated.[50,53] In a preliminary study of 184 patients in sinus rhythm, LA 3DSTE-measured global peak systolic εarea and εarea before and after atrial systole were highly reproducible and compared favorably with LA emptying and active ejection fractions measured from phasic LA volumes.[54] However, spatial and temporal resolution of 3D is considerably less than 2D and image quality may not be adequate and therefore, 3D STE has not achieved wide acceptance.

CMR methods

Volumetric methods

Considered the "gold standard" for assessing cardiac chamber dimensions, CMR provides accurate measurements of LA volume with acceptable temporal resolution (25-50 ms). However, CMR is constrained by increased costs, decreased availability, potential for claustrophobia, an inability to scan patients with intracardiac devices, and problems related to gadolinium contrast. Consecutive multislice short-axis breath-hold acquisitions of the LA using Steady State Free Precession (SSFP) sequences are measured with either manual or automated border detection. Although LA volumes may be measured using biplane area-length methods, this analysis negates an important advantage of CMR over 2D echocardiography. Determination of LA volumes in patients with persistent AF was demonstrated to be feasible, reproducible, and correlate strongly with CCT; in contrast, the correlation with transthoracic echo (TTE)-derived LA volume measurements was only fair to moderate and the inter- and intra-observer agreements with CMR were inferior to the agreement between CCT and CMR.[55] Because absolute LA volumes measured with 2D echocardiography are smaller than those measured with CCT or CMR by 25 and 18% for maximal LA volume, respectively,[55–57] it is important to compare volume estimates to reference values that exist for each imaging modality and not use the different methods interchangeably when serial studies are performed. LA emptying fractions are calculated as they are done for echocardiography, and compared to CMR, TTE overestimates total atrial emptying fraction by 23%.[55]

Volumetric functional analysis from biplane area-length planimetry (total emptying fraction, passive emptying fraction and booster pump emptying fraction) correlated well (r values ranging from 0.52 to 0.81) with feature tracking CMR strain and strain rates (see below) during the reservoir, conduit, and booster pump phases in 10 healthy controls and 10 patients with HFpEF and 10 with hypertrophic cardiomyopathy.[58] Reproducibility for volumetric analysis was not reported in that study. Semi-automated tissue tracking-CMR LA volumes and volumetric emptying fractions were similar to those obtained from manual biplane area-length measurements with good to excellent inter- and intra-observer variability, fair to good inter-study reproducibility, and like the STE tissue tracking study discussed earlier, were half as time consuming.[59]

Several studies have demonstrated the ability of CMR estimates of atrial reservoir, conduit, and contractile functions to predict cardiovascular events. In 1802 participants of the Dallas Heart Study followed for a median of 8.1 years, decreasing CMR-determined total LA emptying fraction (reservoir function) but not LAVi was independently associated with mortality and added incremental power to a predictive model consisting of Framingham risk score, diabetes, race, LV mass and LV ejection fraction.[60] In this large, ethnically diverse cohort, LAVi and total LA emptying fraction were only weakly associated with one another. In another retrospective referral-based cohort study, CMR-estimated LA contractile (booster pump) function was the strongest predictor of major adverse cardiac events and all-cause mortality among 210 patients with chronic hypertension that were without prevalent cardiovascular disease.[61] Finally, in 122 patients referred for dobutamine stress CMR for suspected myocardial ischemia, every 10% decrease in LA passive emptying fraction (conduit function) was associated with a 57% increase in adverse cardiovascular outcomes including death, acute coronary syndrome and CHF hospitalizations over a median follow-up of 23 months, suggesting that reduced LA passive emptying reserve during inotropic stress may be a sensitive marker of ischemia-induced diastolic dysfunction.[62]

Tagged MRI

Tissue deformation can be determined with CMR by using radiofrequency and gradient pulses that null the myocardium at end-diastole, which results in "tissue tags" that can be tracked throughout the cardiac cycle and provide a 3D assessment of regional strain.[63] Tagged MRI is considered the gold standard for myocardial strain, but because of the complexity and lengthy times needed for analysis, it is used primarily in research applications. Tagging the LA is particularly challenging because of its thin walls and not surprisingly, the technique has been limited to ventricular deformation quantitation. An alternative method measures tissue displacement in three dimensions at the pixel level (DENSE, Displacement Encoding with Stimulated Echos) with high spatial resolution. Although post-processing is relatively easy, clinical research with this technique has been limited[64] and has not proved feasible in the LA.

Feature tracking

Feature tracking CMR (FT-CMR) has recently been adapted to quantify cardiac deformation in the left atrium and in validation studies has been shown to be feasible with reproducibility similar to 2D-STE[8,59,65,66] (Figure 7). Figure 7 FT-CMR is a tissue tracking technology like STE that focuses on endocardial and (to a lesser extent) epicardial borders owing to the lack of intra-myocardial features on CMR. Although it possesses high signal-to-noise and contrast-to-noise ratios, FT-CMR has lower in-plane spatial and temporal resolutions than 2D-STE. CMR acquires data over several beats which averages minor beat-to-beat differences; this smoothing coupled with the relatively low temporal resolution may result in an underestimation of strain. Unlike 2D-STE, validation with animal models and well-accepted gold standards (e.g. sonomicrometers) is lacking, and normative data are not as robust (Table 3). Important advantages of FT-CMR are that standard SSFP cine images are used and the method can be applied to clinical data retrospectively. Reproducibility is similar at 1.5 and 3.0 T field strengths. As with 2D-STE, challenges to tissue tracking of the left atrium are the thin atrial walls, the intricate and variable anatomy of the chamber, complex atrial pathophysiology, and the presence of the left atrial appendage and pulmonary veins, which may impair tracking quality. 3D-FT

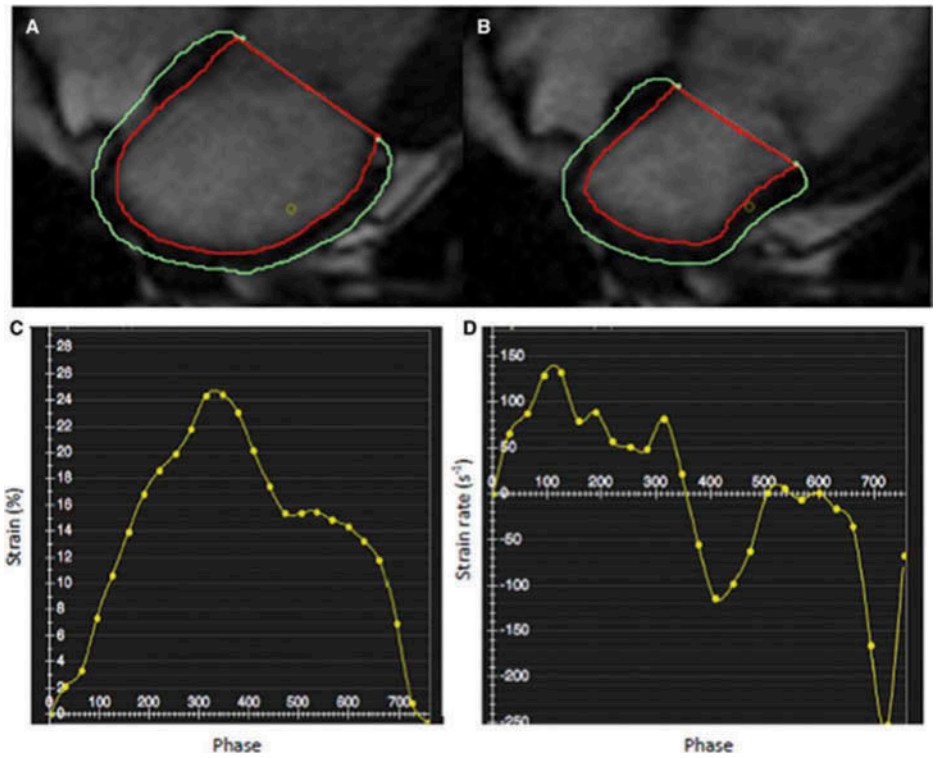

Figure 7. Example of LA feature tracking cardiac magnetic resonance performed on a 4-chamber cine sequence. The atrial wall is marked in all phases, shown here in atrial diastole (A) and atrial systole (B). The region of interest is bounded by the endocardium (red line) and epicardium (green line). Analyses are performed with dedicated analyses, resulting in strain (C) and strain rate (D) curves. (Reproduced from F. J. Olsen et al., Multimodality Cardiac Imaging for the Assessment of Left Atrial Function and the Association With Atrial Arrhythmias, *Circulation: Cardiovascular Imaging*, 9(10), © 2016, with permission from Wolters Kluwer Health, Inc. Permission to reuse must be obtained from the rightsholder.)

can be applied to CMR, but resolution in the through-plane is limiting and has therefore not been widely implemented.[64]

Limited data support the utility of FT-CMR. In one study, LA volumes, FT-CMR (longitudinal) strain and strain rates were measured in 143 participants of the Multi-Ethnic Study of Atherosclerosis who had LGE-detected myocardial scar (replacement fibrosis) that were selected from 2839 participants who were studied with CMR. Compared to 286 matched controls, the scar group had higher minimal (but not maximal) LA volume, lower total LA emptying fraction, maximal strain and strain rate, and early and late diastolic strain rates. Diffuse LV fibrosis (T1 mapping) was significantly associated with reduced LA peak strain and maximal early and late diastolic strain rates,[67] suggesting that diffuse fibrosis is associated with reduced LA functions that precede significant changes in LA size. In a recent elegant study, FT-CMR conduit and booster-pump strains were impaired in 22 patients with HFpEF and conduit strain was strongly associated with peak oxygen consumption on cardiopulmonary exercise testing. On multivariable analysis, conduit strain was the strongest predictor of exercise tolerance both before and after inclusion of LV stiffness and relaxation time measured from conductance catheter-derived LV pressure-volume loops. These data support the hypothesis that LA conduit function reflects intrinsic LA pathology and is not solely due to LV diastolic function.[68]

LGE

Quantitation of LA scar with LGE, which has been validated with electroanatomical mapping and histology, can be used to predict high recurrence rates after RFA[69,70] and assess the effectiveness and completeness of ablative lesions,[71] but a detailed discussion is beyond the scope of this commentary. However, it is important to recognize that there is a significant inverse correlation between the amount of atrial scar and the peak systolic (reservoir) strain.[10] However, the technique is not widely used in daily clinical practice because of the need for specialized training, time-consuming post-processing analyses, the potential for partial volume artifacts, and the limited spatial resolution relative to the thin atrial walls.

Cardiac computed tomography

Volumetric methods

LA volumes can be accurately measured from acquired 3D datasets using CCT.[72,73] However, the radiation exposure and need for iodinated contrast, and the relatively poor temporal resolution of CCT that may preclude accurate measurements of phasic LA volumes and atrial function relegate CCT largely to an important adjunctive role in LA ablation procedures. Compared to CCT, TTE underestimated maximum LA volume by 25% and overestimated total atrial emptying fraction by 14%.[55] Volumetric indices of reservoir and booster pump function were derived from CCT and CMR LA volume-time curves in 54 patients with good overall agreement and a small to moderate bias.[74]

Atrial function measured with CCT volumetric analysis was shown to independently predict mortality after an acute non-ST elevation myocardial infarction (NSTEMI). LA size

and function were measured from CCT coronary angiography in 384 patients followed for a median of 36 months and after adjustments for age, number of diseased coronary arteries, LV EF, and Killip class, both LA total and active (booster pump) emptying fractions, but not LAVi, were significant independent predictors of all-cause mortality.[75]

Tissue tracking CCT

A multimodality 2D tissue tracking algorithm that identifies multiple tracking points representing tissue contours (pixel pattern matching) has been used to derive radial strain measurements that correlate well with radial strain by tagged MRI.[76] While the excellent spatial resolution of CCT is a potential advantage, temporal resolution is relatively poor and the technique has not been applied to the left atrium.

Conclusion

Despite considerable data demonstrating the utility of LA function in predicting cardiovascular events in general and referral populations, and in patients with atrial fibrillation and other heart diseases, risk stratification strategies incorporating these parameters are not currently exploited in clinical practice. There may be several explanations for this paradox. First, irrespective of the methodological technique employed, interpretation of atrial functional indices is complicated because of the interplay between atrial and ventricular functions. Second, LA dysfunction may result from an intrinsic atrial abnormality, altered load, or in an effort to compensate (e.g. a redistribution of reservoir and conduit function in heart failure, or increased atrial contractility owing to Frank-Starling forces in hypertension). Third, atrial dysfunction may have different expressions at different stages of the disease process under study (e.g. peak global strain is increased in mild chronic mitral regurgitation compared to controls, but decreases progressively with increasing grade of severity).[77] Fourth, the methods used to measure LA function all have important limitations and indices from one method (e.g. volumetric) that reflect a specific atrial function often correlate poorly with other methods (e.g. tissue tracking) obtained during the same phase of the cardiac cycle. Finally, the hemodynamic and biophysical properties that are responsible for the functional changes are often assumed, not known.

While tissue tracking (2D-STE and FT-CMR) is increasingly employed, these methods assume that apparent in-plane displacements correspond to actual displacement of tissue, but this neglects the effects of through-plane motion. Another potentially erroneous assumption, at least for FT-CMR, is that detected motion represents tissue, not blood. A major problem relates to suboptimal reproducibility and the lack of standardization, although progress is being made in these areas.[64,78] In addition, deformation analysis requires expertise and highly trained operators, data acquisition and processing steps are time-consuming, and the variable partition values are based on small numbers of subjects, particularly with CMR.

Nevertheless, these increasingly popular measures of atrial function have ignited interest in atrial function in general, and specifically, in atrial reverse remodeling (recently reviewed in Ref. 79). Reverse remodeling has been proposed as an independent prognostic marker in HFpEF[40] and is a potential therapeutic target and endpoint for the evaluation of novel therapies for heart failure[80] in addition to its expanding role in the management of AF.[45,46] Technological improvements in spatial and temporal resolution, automation and other attempts to reduce variability, and standardization among platforms and vendors will enhance the utility of atrial functional analysis.

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