

STATE-OF-THE-ART PAPER

# Left Atrial Size and Function

## Role in Prognosis

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The author examines the ability of left atrial size and function to predict cardiovascular outcomes. Data are sufficient to recommend evaluation of left atrial volume in certain populations, and although analysis of atrial reservoir, conduit, and booster pump function trails in that regard, the gap is rapidly closing. In this state-of-the-art paper, the author reviews the methods used to assess left atrial size and function and discusses their role in predicting cardiovascular events in general and referral populations and in patients with atrial fibrillation, cardiomyopathy, ischemic heart disease, and valvular heart disease. (J Am Coll Cardiol 2014;63:493–505) © 2014 by the American College of Cardiology Foundation

The principal role of the left atrium is to modulate left ventricular (LV) filling and cardiovascular performance by functioning as a *reservoir* for pulmonary venous return during ventricular systole, a *conduit* for pulmonary venous return during early ventricular diastole, and a *booster pump* that augments ventricular filling during late ventricular diastole. It is important to recognize the interplay that exists among these atrial functions and ventricular performance throughout the cardiac cycle. For example, although reservoir function is governed by atrial compliance during ventricular systole (and, to a lesser extent, by atrial contractility and relaxation), it is influenced by descent of the LV base during systole and by LV end-systolic volume (1). Conduit function is influenced by atrial compliance and is reciprocally related to reservoir function but by necessity 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 pre-load), LV end-diastolic pressures (atrial afterload), and LV systolic reserve.

Atrial size and function can be assessed with echocardiography, cardiac computed tomography (CCT), and cardiac magnetic resonance (CMR). Although echocardiography is best suited for these tasks because of its availability, safety, versatility, and ability to image in real time with high temporal and spatial resolution, CCT and CMR are complementary in specific clinical instances (2).

The resurgence of interest in atrial size and function has enhanced our understanding of the atrial contributions to cardiovascular performance in health and disease. Although

the reasons responsible for this renaissance are multifactorial and include the use of left atrial (LA) volume as a biomarker integrating the magnitude and duration of diastolic LV function and the development of sophisticated, noninvasive indexes of LA size and function, the increasingly recognized importance of LA size and function in determining prognosis and risk stratification is critical and is the focus of this state-of-the-art paper.

### Measuring LA Size

Quantifying LA size is difficult, in part because of the left atrium's complex geometry and intricate fiber orientation and the variable contributions of its appendage and pulmonary veins. LA size is most often measured from M-mode and 2-dimensional echocardiography (2DE). Among these measurements, maximal left atrial volume (LAV) indexed to body surface area (LAVi) is most strongly associated with cardiovascular disease and is the most sensitive in predicting cardiovascular outcomes and providing uniform and accurate risk stratification (3). In 317 patients in normal sinus rhythm, LAVi measured from biplane 2-dimensional (2D) apical views was superior to 4-chamber LA area and M-mode LA dimension in predicting the development of first atrial fibrillation (AF), congestive heart failure (CHF), stroke (cerebrovascular accident [CVA]), transient ischemic attack, acute myocardial infarction (AMI), coronary revascularization, and cardiovascular death over 3.5 years of follow-up. In addition, a graded relationship between cumulative event-free survival and the categorical increment of LA size was demonstrated for LAVi. In that study, the ability of LA size to predict cardiovascular events in patients with AF was poor, irrespective of the quantitative method used (3). Despite these data and the American Society of Echocardiography's recommendation of LAVi for the quantification of LA size

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**Abbreviations  
and Acronyms**

- AF** = atrial fibrillation
- AMI** = acute myocardial infarction
- CCT** = cardiac computed tomography
- CHF** = congestive heart failure
- CMR** = cardiac magnetic resonance
- CVA** = cerebrovascular accident
- $\epsilon$**  = strain
- HCM** = hypertrophic cardiomyopathy
- LA** = left atrial
- LAKE** = left atrial kinetic energy
- LAV** = left atrial volume
- LAVi** = left atrial volume indexed to body surface area
- LV** = left ventricular
- MR** = mitral regurgitation
- RT3DE** = real-time 3-dimensional echocardiography
- SR** = strain rate
- STE** = speckle-tracking echocardiography
- TDI** = tissue Doppler imaging
- VTI** = velocity-time integral
- 3D** = 3-dimensional
- 2D** = 2-dimensional
- 2DE** = 2-dimensional echocardiography

(4), individual echocardiography laboratories continue to report a variety of 1-dimensional linear and 2D area measurements (5).

The normal LAVi using echocardiography is  $22 \pm 6 \text{ ml/m}^2$ ; thus, on the basis of the sensitivity and specificity for predicting cardiac events (3,6-8), the American Society of Echocardiography considers LA enlargement as  $>28 \text{ ml/m}^2$  (i.e., 1 SD from the mean). However, for the purpose of identifying LV diastolic dysfunction, an LAV cut point  $>34 \text{ ml/m}^2$  (i.e., 2 SD) was endorsed (9).

Inaccuracies owing to geometric assumptions and foreshortening of the LA cavity with 2D biplane volume methods are overcome with real-time 3-dimensional (3D) echocardiography (RT3DE) (Fig. 1), which has been shown to accurately and reproducibly estimate LAV compared with CMR (10). However, it is difficult to extrapolate cut points derived from the large body of outcome data that were obtained using biplane 2DE, because data using RT3DE are relatively scant. Suh et al. (11) found that RT3DE was a better predictor of cardiovascular events than biplane 2DE in a group of patients with severe LV dysfunction followed for

approximately 1 year; in that study, unlike on 2DE, LAVi on RT3DE was an independent risk factor on multivariate analysis. Caselli et al. (12) also reported a better correlation with major adverse cardiovascular events when LAVs were obtained with RT3DE compared with biplane 2DE in 178 outpatients followed for 45 months. Although these data need to be confirmed, they do suggest a clinically important incremental benefit of risk assessment using RT3DE.

LAVs can be accurately measured from acquired 3D datasets using CCT (13,14). However, the radiation exposure and need for iodinated contrast medium relegate CCT largely to an important adjunctive role in LA ablation procedures; moreover, the relatively poor temporal resolution of CCT may preclude accurate measurements of phasic LAVs and atrial function. CMR (considered the “gold standard”) provides accurate measurements of LAV with acceptable temporal resolution but is limited by increased costs, decreased availability, an inability to measure phasic volumes with gated 3D sequences, and problems related to

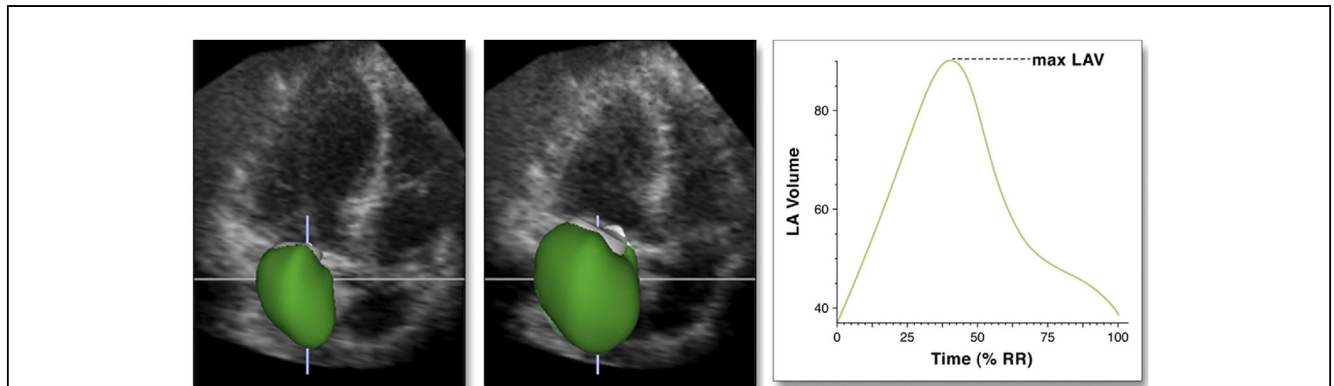
gadolinium contrast and an inability to scan patients with intracardiac devices. Because absolute LAVs measured with 2DE are smaller than those measured with CCT or CMR (15,16), it is important to compare volume estimates with reference values that exist for each imaging modality.

**Assessing LA Functions**

LA function is most often assessed echocardiographically using volumetric analysis; spectral Doppler of transmitral, pulmonary venous, and LA appendage flow; and tissue Doppler and deformation analysis (strain [ $\epsilon$ ] and strain rate [SR] imaging) of the LA body (Tables 1 to 3, Fig. 2). Although atrial pressure-volume loops can be generated in humans using invasive and semi-invasive means (17,18), these methods are cumbersome, time-consuming, and difficult to apply. CMR can quantify scar and has been useful in predicting the risk for recurrence of AF after LA ablation (19). CCT plays an important role in the pre-procedural, intraprocedural, and post-procedural stages of LA ablation. Both CCT and CMR have been used to assess volumetric LA functions (20-26).

**Volumetric methods.** A volumetric assessment of LA reservoir, conduit, and booster pump functions can be obtained from LAVs at their maximums (at end-systole, just before mitral valve opening) and minimums (at end-diastole, when the mitral valve closes) and immediately before atrial systole (before the electrocardiographic P-wave). From these volumes, total, passive, and active ejection (or emptying) fractions can be calculated (Fig. 1, Tables 1 to 3).

**Spectral Doppler.** Doppler waveforms of LA filling (pulmonary venous flow) and LA emptying (transmitral flow) 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 [VTIs]) 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 estimates relative reservoir-to-conduit function. The magnitude and duration of reversed pulmonary flow during atrial contraction is used to estimate atrial contractility and LV diastolic pressures (27). Atrial ejection force, the force exerted by the left atrium to accelerate blood into the left ventricle, is another marker of atrial systolic function (28). LA work can be expressed by left atrial kinetic energy (LAKE), which incorporates LA stroke volume and the transmitral Doppler peak atrial velocity (29). Low LA appendage velocities (usually on transesophageal echocardiography) reflect reduced appendage contractile function and predict the risk for thromboembolism and maintenance of sinus rhythm after cardioversion (30,31). Interpretation of spectral Doppler indexes can be difficult with sinus tachycardia, conduction system disease, and arrhythmia (especially AF), and obtaining high-quality pulmonary venous recordings may



**Figure 1.** Three-Dimensional Rendered Minimal and Maximal LA Volumes and the Volume-Time Curve

Three-dimensional rendering of minimal (**left**) and maximal (**center**) left atrial (LA) volumes that allow accurate measurement of total, passive, and active stroke volumes and calculation of total, passive, and active ejection fractions. (**Right**) Volume-time curve. Reprinted with permission from To et al. (2). LAV = left atrial volume.

be difficult. A major disadvantage of spectral Doppler is its nonspecificity, because changes may be due to LV diastolic dysfunction, mitral valve disease, or abnormal hemodynamic status.

**Tissue Doppler.** Pulsed-wave and color tissue Doppler of atrial contraction ( $A'$ ) provide regional and global (when several sites are averaged) snapshots of atrial systolic function (32,33). Reproducible data with acceptable variability can be obtained with proper attention to technical details. Offline color tissue Doppler waveforms record simultaneously multiple atrial regions and demonstrate an annular-to-superior segment decremental gradient of atrial contraction (33). Tissue velocities during ventricular systole ( $S'$ ) and early diastole ( $E'$ ) correspond to reservoir and conduit function, respectively. However, tissue Doppler velocities are subject to error because of angle dependency and the effects of cardiac motion and tethering and have been superseded by deformation analysis.

**Deformation analysis ( $\epsilon$  and SR imaging).** Strain and SR represent the magnitude and rate, respectively, of myocardial deformation (for a review, see Gorcsan and Tanaka [34]); they can be assessed using either tissue Doppler velocities (tissue Doppler imaging [TDI]) or 2DE techniques (2D speckle-tracking echocardiography [STE]) (Figs. 3 and 4). Both have been used successfully to assess LA global and

regional function (35,36). Although temporal resolution is excellent and ideal 2D image quality is not necessary, TDI is highly angle dependent, and signal-to-noise ratios 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 angle dependency. Frame rates of about 50 to 70 frames/s are needed to avoid speckle decorrelation, and good image quality is needed for accurate tracking. For both modalities,  $\epsilon$  imaging of the left atrium is more difficult and time-consuming than for the left ventricle. Moreover, the far-field location of the atrium, reduced signal-to-noise ratio, the thin atrial wall, and the presence of the appendage and pulmonary vein are challenges in applying deformation analysis to the left atrium.

It is important to recognize that differences in nomenclature used to describe atrial  $\epsilon$  and SR are dependent on whether the atrial or ventricular cycle is used as the reference (i.e., zero baseline) point (Fig. 5). If the ventricular cycle is used, ventricular end-diastole (the QRS complex) is the zero reference, and peak positive longitudinal  $\epsilon$  ( $\epsilon_s$ ) corresponds to atrial reservoir function, and  $\epsilon$  during early and late diastole ( $\epsilon_e$  and  $\epsilon_a$ , respectively) corresponds to conduit and atrial booster function. If the atrial cycle is used, atrial end-diastole (the onset of the P-wave) is the zero reference, and the first negative peak  $\epsilon$  ( $\epsilon_{neg}$ ) represents the atrial booster pump function, positive peak  $\epsilon$  ( $\epsilon_{pos}$ ) corresponds to conduit function, and their sum ( $\epsilon_{total}$ ) represents reservoir function (2,37). SRs in ventricular systole, early diastole, and late diastole (SR-S, -E, and -A, respectively) correspond to reservoir, conduit, and booster pump functions in both schemes.

Although 2D  $\epsilon$  and SR 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 3D

**Table 1.** Volumetric Indexes of LA Function

| LA Function                | LA Volume Fraction  | Calculation                            |
|----------------------------|---------------------|--|
| Global function; reservoir | LA EF (or total EF) | $[(LA_{max} - LA_{min})/LA_{max}]$     |
| Reservoir function         | Expansion index     | $[(LA_{max} - LA_{min})/LA_{min}]$     |
| Conduit*                   | Passive EF          | $[(LA_{max} - LA_{pre-A})/LA_{max}]$   |
| Booster pump               | Active EF           | $[(LA_{pre-A} - LA_{min})/LA_{pre-A}]$ |

\*Conduit volume is actually the volume of blood that passes through the left atrium that cannot be accounted for by reservoir or booster pump function:  $[LV \text{ stroke volume} - (LA_{max} - LA_{min})]$ .

EF = emptying fraction; LA = left atrial;  $LA_{max}$  = maximal left atrial volume;  $LA_{min}$  = minimal left atrial volume;  $LA_{pre-A}$  = left atrial volume immediately before atrial contraction.

**Table 2** Spectral Doppler Indexes of LA Function

| LA Function     | Transmitral Flow     | Pulmonary Venous Flow | Composite Indexes    |
|-----------------|----------------------|-----------------------|----------------------|
| Global function |                      |                       | LAFI                 |
| Reservoir       |                      | S velocity            |                      |
| Conduit         | E velocity, E/A      | D velocity            |                      |
| Booster pump    | A velocity, E/A, AFF | PVa                   | Ejection force, LAKE |

AFF = atrial filling fraction; LA = left atrial; LAFI = left atrial functional index; LAKE = left atrial kinetic energy; PVa = pulmonary venous reversal velocity.

STE overcomes these limitations because it eliminates the effects of through-plane motion that may occur with 2D imaging (37,38). 3D STE is a reproducible technique that more quickly and completely analyzes myocardial deformation (e.g., one can measure longitudinal and circumferential  $\epsilon$  from the same 3D dataset) and enables the evaluation of LA endocardial area  $\epsilon$  (earea, longitudinal times circumferential  $\epsilon$ ) (38,39). In a preliminary study of 184 patients in sinus rhythm, LA 3D STE-measured global maximal earea and earea before atrial systole were highly reproducible and compared favorably with LA emptying and active ejection fractions measured from phasic LAVs (40).

**Prognosis and Risk Stratification Using Atrial Volume and Function**

**Risk prediction in general and referral populations.** Indexes of LA size are markers of cardiovascular risk in the general population (7,41-43). The strength of the association between atrial remodeling (i.e., increased LAVi) and cardiovascular risk is influenced by the nature of the population under study. For example, in a cohort of 1,160 elderly patients from Olmsted County, Minnesota, with cardiovascular disease referred for echocardiography, both LAVi and LV diastolic dysfunction were independently predictive of cardiovascular events (first AMI, coronary revascularization, AF, CHF, transient ischemic attack, CVA, or cardiovascular death) (44), and in a clinical study of 314 patients with AMIs with 15-month follow-up, LAVi powerfully predicted mortality after adjustment for Doppler parameters of diastolic dysfunction (45). However, in a study of 2,042 randomly selected residents of Olmsted County, LAVi lost the ability to predict all-cause mortality when controlling for the degree of diastolic dysfunction,

suggesting that in the general population, changes in LAVi are closely related to diastolic function and therefore provide no incremental predictive benefit (41). Although most of the subjects in studies that examine the prognostic value of LA size are elderly, Leung et al. (46) studied a large (n = 483), unselected series of younger (mean age 47 years) patients in sinus rhythm referred for echocardiography and followed for a median of 6.8 years; LAVi  $\geq 24$  ml/m<sup>2</sup> was the only independent echocardiographic predictor (including Doppler transmitral diastolic flow profiles) of cardiovascular death, CVA, CHF, AMI, and AF and was incremental to clinical predictors.

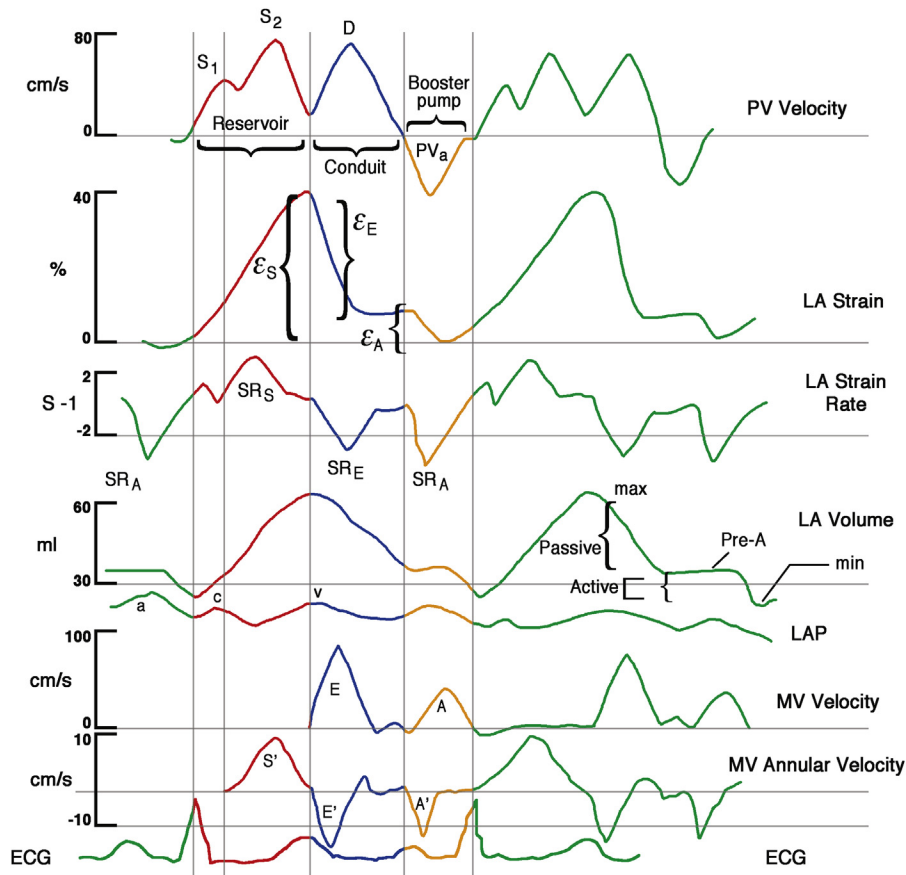
Supporting the importance of the type of population under study and confirming the prognostic importance of LA function in the general population, decreasing LA emptying fraction (EF) but not LAVi (measured with CMR) was independently associated with mortality and added incremental power to a predictive model consisting of Framingham risk score, diabetes, race, LV mass, and LV ejection fraction in 1,802 participants of the Dallas Heart Study followed for a median of 8.1 years (47). In this large, ethnically diverse cohort, LAVi and LA EF were only weakly associated with each other. In another important investigation, both echocardiographic LAVi and LA EF were shown to be powerful predictors of new-onset AF and atrial flutter in 574 elderly participants referred for echocardiography and followed prospectively for a mean of 1.9 years. LA EF was associated with increased risk after adjustment for baseline clinical risk factors, LV ejection fraction, LV diastolic functional grade, and LAV. Patients at highest risk were those with both LA emptying fractions  $\leq 49\%$  and LAVi  $\geq 38$  ml/m<sup>2</sup> (48). That LA emptying fraction was superior and incremental to LAV suggests that reservoir function of the left atrium represents a more advanced state of LA remodeling and perhaps underlying LV dysfunction than LA enlargement alone. This is a theme permeating many prognostic studies of LA function.

Several studies suggest that atrial booster pump function also identifies cardiovascular risk in the general population (25,49-51). A low transmitral Doppler atrial filling fraction (and increased E/A<sub>V<sub>TI</sub></sub>) predicted new-onset AF in 942 subjects of the Framingham study independent of LA size; thus, a 1 SD decrease in the atrial filling fraction was associated with a 28% higher risk for AF, suggesting that decreased booster pump function pre-dates atrial arrhythmia (49). Tissue Doppler annular velocity after atrial contraction (A') was a significant independent predictor of cardiac mortality in 518 subjects (353 with a variety of cardiac diseases) after 2 years; when A' was  $\leq 4$  cm/s, the hazard ratio of cardiac death was significantly greater than when it was  $>7$  cm/s (50). In an unselected cohort of 2,808 subjects from the Strong Heart Study with a high prevalence of obesity and diabetes (but not prevalent cardiovascular disease), LA systolic (ejection) force was associated with a higher rate of combined fatal and nonfatal cardiovascular

**Table 3** Tissue Doppler and Deformational Indexes of LA Function

| LA Function  | Tissue Velocity | Strain                         | Strain Rate |
|--------------|-----------------|--------------------------------|-------------|
| Reservoir    | S'              | $\epsilon_s, \epsilon_{total}$ | SR-S        |
| Conduit      | E'              | $\epsilon_e, \epsilon_{pos}$   | SR-E        |
| Booster pump | A'              | $\epsilon_a, \epsilon_{neg}$   | SR-A        |

$\epsilon$  = strain; LA = left atrial; neg = negative; pos = positive; SR = strain rate.



**Figure 2** Functions of the Left Atrium and Their Color-Coded Relation to the Cardiac Cycle

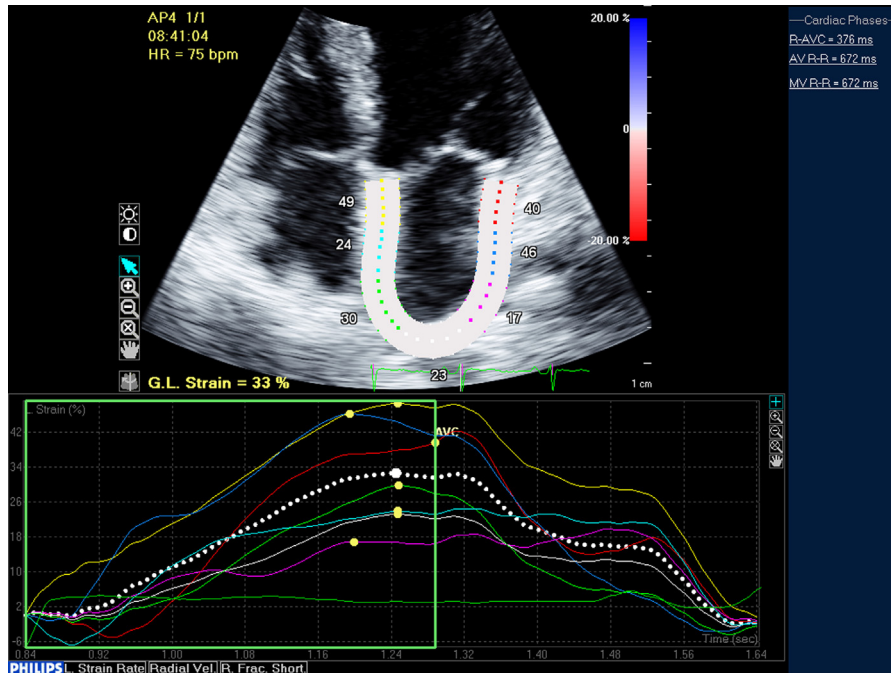
Displayed are pulmonary venous (PV) velocity, left atrial (LA) strain ( $\epsilon$ ), LA strain rate (SR), LA volume, left atrial pressure (LAP), and mitral spectral and tissue Doppler. Reservoir, conduit, and booster pump functions are denoted by red, blue, and yellow lines, respectively. Figure illustration by Craig Skaggs. ECG = electrocardiogram; MV = mitral valve.

events, independent of age, risk factors, LV geometry, and diastolic functional grade (51). Finally, in a retrospective referral-based cohort study, LA contractile function (and the proportional contribution from atrial contraction to total diastolic filling measured with CMR) was the strongest predictor of major adverse cardiac events and all-cause mortality in 210 patients with chronic hypertension but no prevalent cardiovascular disease (25).

Although the large body of data discussed here support the use of maximal LAV for predicting cardiovascular risk, theoretical considerations regarding atrial function and loading and a growing body of research suggest that minimal LAV may be a more important prognostic indicator (12,27,52,53). Minimal LAV is measured at end-diastole after being exposed to LV diastolic pressure (therefore accounting for atrial afterload) and is closely related to LA maximal elastance (a load-independent measure of atrial contractility) (54), whereas LA maximal volume is due primarily to increased atrial pressure and volume. The correlation between LV filling pressures was stronger for minimal than maximal LAV in 70 patients undergoing

cardiac catheterization; in that study, a minimal LAV >40 ml was sensitive and specific (82% and 98%, respectively) for identifying a pulmonary capillary wedge pressure >12 mm Hg (27). In a prospective study of 574 participants in Olmsted County, minimal LAV was superior for predicting the 3-year risk for developing first AF or atrial flutter and was an independent predictor in a model that included clinical variables, body mass index, diastolic dysfunction, and maximal LAV (53). Finally, in 178 outpatients referred for clinically indicated echocardiography who underwent 2D echocardiography and RT3DE and were followed for a median of 45 months, minimal LAV on RT3DE was the best independent predictor in a multivariate analysis of major adverse cardiovascular events (12). Surprisingly, 2D maximal and minimal LAVs were not predictive of death, CVA, or AMI; this may have been due to the low frequency (17%) of events and the variable clinical background and risk profile of the patients.

**Risk prediction in patients with AF.** LA enlargement and dysfunction (reduced reservoir and conduit function, reduced or absent booster pump function) are common in



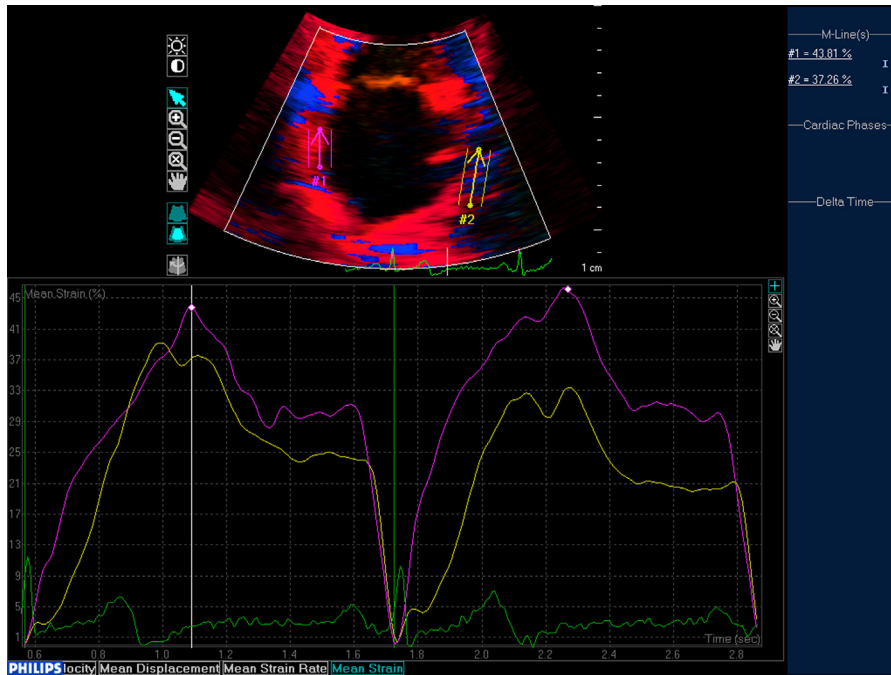
**Figure 3** Example of STE-Derived LA Strain

Regional strains are denoted by the **colored lines** and global longitudinal (G.L.) strain by the **white dotted line**. The **closed circles** on each regional strain-time curve identify peak strain. AP4 = apical 4-chamber; AV = aortic valve; AVC = aortic valve closure; HR = heart rate; STE = speckle-tracking echocardiography; other abbreviations as in Figure 2.

patients with AF and are able to predict cardiovascular events (38,55–58). In a small case-control study, Saha et al. (59) showed that global longitudinal LA es and LA EF were reduced and maximal and minimal LAVs were increased in 36 patients with nonvalvular AF compared with 41 controls; global LA es was the only echocardiographic variable associated with greater odds of having a CHADS<sub>2</sub> score  $\geq 2$ . Moreover, the addition of global LA es and LAVi to statistical models was incremental to the CHADS<sub>2</sub> score in predicting hospitalization and/or death. In a retrospective, registry-based case-control study comparing 57 patients with paroxysmal AF and low-risk CHADS<sub>2</sub> scores ( $\leq 1$  before their index CVA or transient ischemic attack) with 57 AF controls, reduced es and ea predicted stroke risk (60). In a small study of 46 patients with well-documented lone AF followed for 1,296 patient-years (median 27 years), those with LAVi  $\geq 32$  ml/m<sup>2</sup> at baseline or during follow-up (i.e., indicating a measurable pathophysiological change in the atrium) had worse event-free survival after adjustment for age and clinical risk factors, suggesting that the increased risk could not be attributed to AF or age alone (61). In another study, peak LA longitudinal ea and peak SRs during the reservoir (SR-S) and conduit (SR-E) phases were significantly less (in absolute terms) in permanent AF patients with (n = 20) compared with those without (n = 46) previous CVAs; controlling for age, LAVi, and LV ejection fraction, ea and

SR-S were independently associated with CVA, supporting the hypothesis that atrial remodeling and impaired atrial contractility may lead to greater stasis and a greater risk for thromboembolism (62). Larger prospective studies are needed to confirm this tantalizing hypothesis.

Assessment of LA function has been useful to predict the success of restoring sinus rhythm in patients with AF after either direct-current cardioversion or AF ablation. Di Salvo et al. (57) predicted the 9-month recurrence rate in 65 patients with recent-onset lone AF after successful cardioversion with tissue Doppler velocities and  $\epsilon$  and indexes from transthoracic (including LAVs and LA reservoir index) and transesophageal (LA appendage peak velocity) echocardiography. The best predictors of sinus rhythm maintenance were atrial inferior wall peak SR-S  $> 1.8$  s<sup>-1</sup> and atrial septal peak es  $> 22\%$ ; these measures of atrial reservoir capacity predicted independently the maintenance of sinus rhythm. Although es (measured in the basal LA wall) was not predictive of recurrence in a study of 46 patients with AF, the change in LA es after cardioversion was significantly higher among patients who maintained sinus rhythm (63). Illustrative of the methodological variability confounding studies of atrial function, LA enlargement and decreased SR-E independently predicted failure of cardioversion or return to AF after 4 weeks in 42 patients studied before cardioversion (64), and in a prospective study of 130 patients undergoing cardioversion for AF, atrial



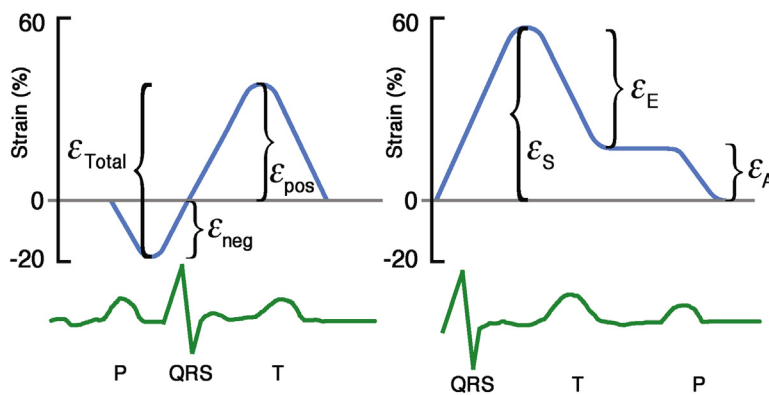
**Figure 4** Example of Tissue Doppler Imaging Left Atrial Strain

Strain curves for the inferior (purple) and anterior (yellow) segments are shown.

asynchrony (quantified as the standard deviation of the time to peak  $\epsilon$  using a six-segment model of the left atrium) was an independent predictor of recurrence, whereas LAV was not (65). Thus, although the specific deformational parameters vary among these small studies, abnormalities of the magnitude and timing of atrial deformation consistently predict recurrences of AF after cardioversion.

Similar results are seen after catheter ablation for AF. For example, 74 patients with paroxysmal and 44 patients with

persistent AF underwent TDI  $\epsilon$  studies before and after ablation and during a 3-month follow-up period. Atrial deformation parameters during systole and late diastole discriminated patients who maintained sinus rhythm after catheter ablation from those with recurrence, increased in patients who maintained sinus rhythm, and were more compromised in patients with persistent than paroxysmal AF (56). The partition values that best predicted sinus rhythm maintenance were septal and inferior SR-S  $>2.25 \text{ s}^{-1}$  and



**Figure 5** 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. Figure illustration by Craig Skaggs.  $\epsilon$  = strain.

inferior  $\epsilon_s > 19.5\%$ . Similar data were reported by Hammerstingl et al. (66) using 2D STE. That the changes after ablation are likely to reflect the atrial reverse remodeling is supported by Kuppahally et al. (19), who showed that patients with mild ( $< 10\%$ ) structural remodeling (i.e., fibrosis) by delayed enhancement CMR had greater increases in STE-determined LA  $\epsilon_s$  and SR-S after ablation and less recurrences at 12 months compared with patients with moderate to severe ( $> 10\%$ ) structural remodeling. In addition,  $\epsilon_s$  at baseline was an independent predictor of reverse remodeling (defined as a  $\geq 15\%$  reduction in maximal LAV) in a study of 148 patients undergoing ablation for AF (67).

**Risk prediction in patients with cardiomyopathy.** LAV is a predictor of the development of new heart failure irrespective of LV systolic function (7,42), and once heart failure is present, LA enlargement and dysfunction are important predictors of clinical outcomes in patients with dilated cardiomyopathy. LA dimension was a significant predictor of mortality and CHF hospitalization after adjusting for LV ejection fraction, New York Heart Association functional class, etiology, and type of study (registry vs. trial) in 1,172 patients enrolled in the SOLVD (Studies of Left Ventricular Dysfunction) trials (68). LA area was a powerful predictor of death or hospitalization for heart failure independent of age, New York Heart Association functional class, LV ejection fraction, and restrictive filling pattern in 1,157 patients from the prospective MeERGE (Meta-Analysis Research Group in Echocardiography) collaboration, a meta-analysis of 18 heart failure studies (69). Similarly, in 337 patients with dilated cardiomyopathy, maximal LAV predicted death and transplantation over a mean follow-up period of 41 months, independent of AF, LV volume, LV ejection fraction, mitral regurgitation (MR), and transmitral E/A ratio; those with maximal LAVs  $> 38.5 \text{ ml/m}^2$  yielded a risk ratio of 3.8 (70). In another study, LAV<sub>i</sub> was an independent predictor for cardiac events in 146 patients hospitalized for heart failure followed for a median of 448 days; there was a stepwise increase in the risk for cardiac events for each increment of LAV<sub>i</sub>, further confirming the value of LAV<sub>i</sub> in stratifying risk in patients with heart failure (71). A similar independent prognostic value for LAV was demonstrated in 192 patients with Chagas' cardiomyopathy (72). In the Heart and Soul Study, LAV<sub>i</sub> was measured in 935 ambulatory patients with coronary disease but without atrial arrhythmias or significant mitral valve disease. LAV<sub>i</sub>  $> 50 \text{ ml/m}^2$  was able to predict CHF hospitalization and mortality as well as the LV ejection fraction (73). Finally, in a study alluded to earlier (11), 3D LAV  $> 100 \text{ ml}$  predicted 1-year adverse cardiovascular outcomes among patients with severe LV dysfunction. Thus, a considerable body of data exists to support the incorporation of LA size in risk stratification schemes in patients with dilated cardiomyopathy.

However, few data support the measurement of atrial function to predict cardiovascular outcomes in these patients,

although abnormalities and compensatory features of reservoir, conduit, and booster pump functions are described (74-76). LA work estimated by LAKE was independently predictive of cardiovascular death and hospitalization for CHF in 243 heart failure patients (the reference value of LAKE derived from 230 controls was  $5.4 \text{ kdynes/m}^2$ ) followed for a median of 3.1 years. Interestingly, maximal LAV was not an independent predictor, perhaps because maximal and minimal LAVs are incorporated in the formulation of LAKE. Importantly, Doppler evidence of severe LV dysfunction (grades 3 and 4) were excluded because they invalidate the measurement of LA work (77).

LA enlargement is a marker of disease severity and predicts adverse cardiovascular events in patients with hypertrophic cardiomyopathy (HCM) (78-81). Sixty-one HCM patients with LAV<sub>i</sub>  $> 34 \text{ ml/m}^2$  had a significantly higher incidence of serious cardiovascular events (16.4% vs. 2.3%) than 43 patients with smaller LAV<sub>i</sub> but also had worse MR, greater hypertrophy, and more diastolic dysfunction (78). LAV<sub>i</sub> (and an estimate of diastolic function, E/E') was an independent predictor of cardiovascular mortality, CHF hospitalization, and CVA in 454 patients with apical cardiomyopathy (79), and major adverse cardiovascular events (CVA, CHF, and sudden death) occurred more often in patients with increased maximal and minimal LAVs in 102 patients with nonobstructive HCM (21 with apical hypertrophy) followed for a median of 30.8 months (80). In the latter study, LAV<sub>i</sub> was an independent predictor of events, and event-free survival was significantly reduced using a partition value of  $41 \text{ ml/m}^2$ .

Not surprisingly, atrial function is abnormal in HCM. Increases in booster pump function and impaired reservoir and conduit functions have been reported (81,82), and a variety of abnormalities in atrial function have been reported using tissue Doppler and deformational analysis (83-85); methodological differences and differences in the type and stage of disease are likely responsible for the variable results. The ability of atrial function to predict cardiovascular events in HCM has not been studied.

**Risk prediction in patients with ischemic heart disease.** A number of studies have shown that LAV predicts survival after AMI (45,86,87). In 314 patients with AMIs followed for a mean of 15 months, LAV<sub>i</sub>  $> 32 \text{ ml/m}^2$  was a powerful predictor of all-cause mortality and was incremental to clinical information and LV function (45). Beinart et al. (86) reported that patients ( $n = 63$ ) with AMIs and LAV<sub>i</sub>  $> 32 \text{ ml/m}^2$  measured within 48 h of admission had a higher incidence of CHF and MR, increased LV dimensions, and reduced LV ejection fraction at baseline and a higher 5-year mortality rate (34.5% vs. 14.2%) compared with patients ( $n = 72$ ) with smaller atria. In addition to clinical variables, LAV<sub>i</sub>  $> 32 \text{ ml/m}^2$  and diastolic dysfunction were independent predictors of 5-year mortality. LAV<sub>i</sub> at baseline was also an independent predictor of all-cause mortality and heart failure hospitalization in the 640 patients with LV dysfunction, CHF, or both after AMI comprising the



VALIANT Echo (Valsartan in Acute Myocardial Infarction Trial Echocardiography) study. Moreover, LA enlargement during the first month (early LA remodeling) was significantly greater in patients with than without events (87).

Indexes of atrial function have also been shown to predict cardiovascular events in patients with ischemic heart disease. Atrial function measured with volumetric analysis was an independent predictor of mortality after an acute non-ST-segment elevation myocardial infarction. LA size and function were measured from cardiac computed tomographic coronary arteriography in 384 patients followed for a median of 36 months; after adjustments for age, number of diseased coronary arteries, LV ejection fraction, and Killip class, both LA EF and active (booster pump) ejection fraction, but not LAVi, were significant independent predictors of all-cause mortality (23). In another study, baseline (within 72 h of admission) atrial functional variables, including TDI measurement of mean (average of 4 segments) LA atrial conduction velocity, were measured in 164 patients with non-ST-segment elevation acute coronary syndromes and were followed for 6 months. LA atrial conduction velocity <6.3 cm/s was an independent predictor of cardiac mortality and/or rehospitalization for recurrent acute coronary syndrome or CHF and was incremental to clinical data, LV ejection fraction, and LV diastolic function for predicting events. In contrast, LAVi, active LA ejection fraction, transmitral A velocity, and septal annular A' were not different between the 33 patients with and the 131 patients without cardiac events (88). LA EF independently predicted death, reinfarction, CVA, and CHF admission and provided incremental prognostic information to maximal LAV in 199 patients in whom CMR was performed within 1 to 3 days of an ST-segment elevation myocardial infarction and who were followed for a median of 2.3 years (89). Similarly, LA  $\epsilon$ s and maximal LAV measured within 48 h of an AMI were independent predictors of all-cause mortality, reinfarction, and CHF hospitalization after adjusting for clinical and echocardiographic parameters in 320 patients with AMIs followed for a mean of 27 months (90). The same investigators found that maximal LAV and  $\epsilon$ s were independent predictors of LA remodeling ( $\geq 8$  ml/m<sup>2</sup> increase in maximal LAV); in contrast to those without remodeling, those with LA remodeling had worsening of LA  $\epsilon$ s and SR-S (91). Finally, in the largest study to date, peak LA  $\epsilon$ s measured within 48 h of admission was significantly related to the composite outcome of death and CHF in a study of 843 patients with AMIs followed for a median of 23 months. However, this effect was not independent after adjusting for global LV longitudinal  $\epsilon$ , maximal LAV, and age, suggesting that LA  $\epsilon$ s represents a composite of longitudinal LV systolic function and maximal atrial volume (92).

In 122 patients referred for dobutamine stress CMR for suspected myocardial ischemia, every decrease in LA passive emptying fraction (a surrogate of conduit function) of 10% was associated with a 57% increase in adverse cardiovascular

outcomes, including death, acute coronary syndrome, and CHF hospitalizations over a median follow-up period of 23 months, suggesting that reduced LA passive emptying reserve during inotropic stress may be a sensitive marker of ischemia-induced diastolic dysfunction (93). A novel measure of atrial function, the LA functional index ([LA EF  $\times$  LV outflow tract VTI]/LAVi), was studied in 855 patients with coronary artery disease and LV ejection fractions  $\geq 50\%$  followed for a median of 7.9 years as part of the Heart and Soul Study. Each SD decrease in LA functional index was associated with a 2.6-fold increase in the hazard of adverse cardiovascular events (94). Taken together, these studies support the contention that assessment of LA size and function refine risk stratification models in acute and chronic ischemic heart disease.

#### **Predicting risk in patients with valvular heart disease.**

LA enlargement resulting from volume overload is common in chronic MR and reflects both the severity and duration of regurgitation (95). Although it is recognized that there is a close relation between LA size and mortality after mitral valve surgery (96) and the combined endpoint of mortality, need for surgery, and development of AF (97), the ability of LA enlargement to predict outcomes in chronic organic MR managed medically is less clear. The relation between LA diameter and mortality in MR owing to flail leaflets treated medically and surgically was examined in 788 patients in sinus rhythm registered in the MIDA (Mitral Regurgitation International Database) registry (98). LA diameter  $\geq 55$  mm was associated with lower 8-year survival and independently predicted overall mortality and cardiac mortality in both symptomatic and asymptomatic patients under medical treatment, respectively. In operated patients, LA diameter  $\geq 55$  mm was associated with greater survival but had no impact on the post-operative outcome (98). The more predictive LAV was available in a study by Le Tourneau et al. (99), who prospectively examined 492 patients with chronic organic MR in sinus rhythm. In that study, LAVi was independently associated with 5-year survival; patients with LAVi  $\geq 60$  ml/m<sup>2</sup> treated medically had increased mortality and more cardiac events (AF and heart failure) than those with LAVi <40 ml/m<sup>2</sup>. The 5-year survival rates in conservatively managed patients with LAVi  $\geq 60$ , 40 to 59, and <40 ml/m<sup>2</sup> were  $53 \pm 8.6\%$ ,  $84 \pm 4.8\%$ , and  $90 \pm 3.0\%$ , respectively. After mitral valve surgery, LAVi  $\geq 60$  ml/m<sup>2</sup> lost its prognostic value (99).

Only a few studies examined the prognostic power of atrial function in patients with chronic MR. Peak global  $\epsilon$ s is increased in patients with mild chronic MR compared with controls but decreases progressively with increasing grade of severity (100). Phasic LAVs were higher and  $\epsilon$ s and SR-S, -E, and -A were increased in 27 MR patients compared with 25 controls; however, the active ejection fraction was no different, and the tissue velocity A' was reduced in MR, suggesting reduced contractile contribution to filling despite increased atrial myocardial deformation (101). In a small study of 53 patients in sinus rhythm undergoing mitral

valve surgery for severe MR, peak LA  $\epsilon$ s and LAVi were independent predictors of post-operative AF (102). In 150 patients undergoing Maze procedures who maintained sinus rhythm, the absence of LA active contraction (absent A wave on transmitral Doppler) and LAVi  $\geq 33$  ml/m<sup>2</sup> at baseline were associated with independent 5- and 3-fold increases in the risk for CVA, respectively (103).

Mitral stenosis is associated with LA remodeling, increased LA stiffness, and abnormal atrial contractility. In 53 patients with asymptomatic rheumatic mitral stenosis (mean mitral valve area  $1.5 \pm 0.4$  cm<sup>2</sup>) followed for 3 years, LAV was nonsignificantly increased, and TDI mean SR-S significantly decreased in patients with clinical events (symptoms, hospitalization, AF, thromboembolic events, valve surgery, or percutaneous valvuloplasty) compared with those without events; the LA ejection fraction and the LA expansion index were similar in both groups. The best independent predictor of events was SR-S; a cutoff value of  $-1.69$  s<sup>-1</sup> was predictive of events with sensitivity and specificity of 88% and 80.6%, respectively (104). These investigators later showed that LA peak  $\epsilon$ s was the best predictor of AF over 4 years in 101 asymptomatic patients with isolated rheumatic mitral stenosis (105). These data suggest that the degree of underlying atrial remodeling with associated impaired reservoir capacity (i.e., atrial stiffness) can predict the development of symptoms and cardiovascular events independent of mitral valve area.

Preserved (or compensatory increased) atrial booster pump function is important for the maintenance of cardiac output in aortic stenosis. Interestingly, in 64 patients with severe aortic stenosis, all speckle-tracking echocardiographic  $\epsilon$ -based parameters were reduced compared with 20 healthy controls. Moreover, although all phasic LAVs increased, LA active ejection fraction decreased, and the deformational parameters and phasic volumes correlated poorly (106). Rossi et al. (107) showed that LA diameter predicted independently post-operative symptomatic alleviation after valve replacement for severe isolated aortic stenosis. In a recent, more methodologically robust study, peak  $\epsilon$ a increased and LAVi decreased 40 days after aortic valve replacement for severe aortic stenosis; the only independent predictor of improved atrial size and function was the severity of the mean aortic gradient (108). The investigators suggested that early identification of LA enlargement and dysfunction might contribute to better patient recruitment and more beneficial valve surgery.

## Perspectives

Despite considerable data demonstrating the utility of LA size and function in predicting incrementally cardiovascular events, risk stratification strategies incorporating these parameters are not currently exploited in clinical practice. Several reasons may be responsible. Although 3D techniques overcome many of the difficulties confounding the 2D assessment of atrial size, atrial function remains problematic

because of the interplay between atrial and ventricular function that complicates analysis, irrespective of the methodological technique. Moreover, LA enlargement and dysfunction may result from an intrinsic atrial abnormality, altered load, or compensation (e.g., a redistribution of reservoir and conduit function, increased atrial contractility owing to Frank-Starling forces) and may have different expressions at different stages of the disease process under study. The methods used to measure LA function all have important limitations, and indexes that reflect specific atrial functions often correlate poorly with others obtained during the same phase of the cardiac cycle. Most often, the hemodynamic and biophysical properties that are responsible for the functional changes are assumed, not known. Although  $\epsilon$  and SR are increasingly used, the left atrium offers unique challenges to its use. Deformation analysis requires expertise and highly trained operators, and the data acquisition and processing steps are time-consuming. Variable partition values, the variability in values among the different speckle-tracking echocardiographic algorithms, rapidly changing software, and a paucity of normative values remain impediments to the use of  $\epsilon$  imaging. In addition, most cutoff values are based on small numbers of subjects, are highly variable, and are dependent on age, sex, atrial region, and ultrasound manufacturer.

## Conclusions

The studies discussed in this review support the contention that LAVi is ready to be incorporated into risk stratification and decision-making strategies. It is clear that studies of LA function provide new insights into the contribution of LA performance to cardiovascular disease and are promising tools for predicting cardiovascular events in a wide range of patient populations. Considerable data also support the use of LA EF for predicting events. However, robust clinical outcome data from large prospective outcome trials are needed to confirm the incremental predictive ability of other measures (e.g., deformation) of LA function. Also needed are standardization of equipment and analytic techniques, development of age- and sex-adjusted normal reference values on a larger scale, and studies to determine the impact of therapies that reverse remodel the left atrium and improve LA function on clinical outcomes.

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**Key Words:** cardiovascular outcomes ■ left atrial function ■ left atrial volume.