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# Clinical Implications of Left Atrial Enlargement: A Review

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## ABSTRACT

Echocardiographically determined left atrial (LA) size has been shown to be a significant predictor of cardiovascular (CV) outcomes. We review the physiology and echocardiographic assessment of LA size and functions and describe the pathophysiologic determinants and clinical implications of LA enlargement. However, despite strong evidence, standardized LA size assessment and generalized applicability of its clinical implications to patient care have yet to be determined. Nevertheless, current findings suggest that echocardiographically determined LA size may become an important clinical risk identifier in preclinical CV disease and should be assessed as a part of routine comprehensive echocardiographic evaluation.

## INTRODUCTION

Strong evidence suggests that the presence of left atrial (LA) enlargement portends a clinically significant risk of adverse cardiovascular (CV) outcomes for the patient. Substantial biologic plausibility supports the prognostic significance of LA size. However, to maximize the utility of LA size, which is represented more accurately by LA volume than M-mode LA dimensions,[1] an understanding of LA enlargement and its association with preclinical CV disease is important.

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## LA FUNCTIONS

The LA functions in three phases within the cardiac cycle: 1) as a ''reservoir'' that receives blood from the pulmonary venous circulation during ventricular systole and isovolumetric relaxation; 2) as a ''conduit'' for transfer of blood into the left ventricle (LV) during the early phase of ventricular diastole, after mitral valve opening via a pressure gradient, and through which blood flows passively from the pulmonary veins into the LV during ventricular diastasis; and 3) as a ''contractile'' chamber that actively empties blood into the LV immediately before the onset of LV systole and establishes the LV end diastolic volume. This ''booster pump'' function of LA contributes to the cardiac output that only accounts for approximately 20% of LV stroke volume but becomes significantly important in the setting of severe LV dysfunction. These reservoir, conduit, and contraction functions of the LA mechanically facilitate the transition between the almost continuous flow through the pulmonary venous circulation and the intermittent filling of the LV.

The relative contribution of LA phasic function to LV filing is dependent on the LV diastolic properties and therefore influenced by the same factors that affect LV diastolic functions.[2] The relative importance of LA functions varies in accordance to the LV filling profile: LA reservoir and pump functions predominate in patients with a slow relaxation LV filling pattern, whereas LA conduit function predominates in patients with a restrictive LV filling pattern.[2] These observations are consistent with a LA Starling mechanism being operative in early-stage LV filling impairment and becoming inefficient in end-stage LV filling impairment.

Although only maximum LA volume is routinely measured, assessment of various LA phasic volumes can be used to describe LA functions. LA volumes generally are measured at three points: 1) just before mitral valve opening (maximum LA volume, or $Vol_{max}$); 2) at the onset of the P-wave on electrocardiography (preatrial contraction volume, or $Vol_p$); and 3) at mitral valve closure (minimal LA volume, or $Vol_{min}$). The LA emptying parameters are derived as:

LA passive emptying volume = ($Vol_{max} - Vol_p$);

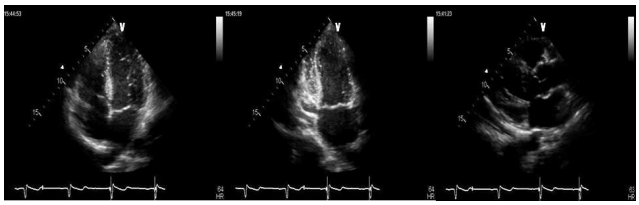

**Figure 1. Echocardiographic assessment of left atrial volume.**

LA conduit volume = LV stroke volume − ($Vol_{max}$ − $Vol_{min}$);
LA active emptying volume = ($Vol_p$ − $Vol_{min}$); and LA total emptying volume = ($Vol_{max}$ − $Vol_{min}$).[3]

## ASSESSMENT OF LA SIZE

Echocardiographic assessment of LA size is a measurement of its anteroposterior linear dimension by M-mode or two-dimensional echocardiography in parasternal long axis view.[4,5] Although this one-dimensional measurement has been shown to correlate with angiographic measurements and has been used extensively in clinical and research work, it is a less accurate and unreliable representation of the true LA size.[6,7] Assessment of LA by linear measurements assumes the constant relationship between all LA dimensions, which may not be true, especially in the presence of asymmetric LA enlargement in superior-inferior and medial-lateral axis. Therefore, current guidelines recommend determination of LA volume for assessment of LA geometry.[1] In contrast to LA dimensions, LA volume assessment by two- or three-dimensional echocardiography provides a more accurate and reproducible estimation of LA size, when compared with reference standards such as magnetic resonance imaging (MRI), biplane contrast ventriculography, and cine computed tomography (CT).[6,8–11] In addition, the strength of the association between CV diseases and LA size is stronger for LA volume than for LA linear dimension.[12,13]

The simplest method of LA volume estimation is the cube formula, which has proven to be inferior to other methods. At present, the American Society of Echocardiography, in conjunction with the European Association of Echocardiography, recommends either the ellipsoid model or the Simpson's method for LA volume estimation (Figure 1).[1] The biplane area-length method, a modification of the ellipsoid method, has been used in the majority of research and clinical studies and is the recommended ellipsoid method. Recently, LA volume has been measured using three-dimensional echocardiography and has shown good correlation with other methods, including MRI.[14] Magnetic endocardial catheter mapping has also been used for LA volume assessment.[15] Despite these methods with promising accuracy, there is no consensus on the specific method that should be used to estimate LA volume. However, even though the echocardiographic methods underestimate LA volume when compared to CT[9] or MRI,[11] echocardiographic estimation of LA volume is preferred in clinical settings because of its portability and safety.

Normal indexed LA volume has been determined using the preferred biplane techniques (area-length or method of disks) in several studies to be 22 ± 6 mL/$m^2$.[1]

## ASSESSMENT OF LA FUNCTION

Doppler evaluation of transmitral and pulmonary venous blood flow velocities is routinely used for LA function assessment. Pulmonary vein Doppler shows four distinct velocity components (two systolic velocities, PVs1 and PVs2; diastolic velocity, PVd; and atrial flow reversal velocity, PVa). Apart from PVs2 (mid-late ventricular systolic flow), the remaining pulmonary vein flow velocities follow phasic changes in LA pressure.[16] The magnitude and velocity-time integral of systolic velocities represents LA reservoir functions,[17] while PVd reflects LA conduit functions.[18] As LA contraction empties blood into the LV and pulmonary veins, LA contractile functions can be assessed by pulmonary venous blood flow and transmitral flow (A-wave velocity, A-wave velocity-time integral, and atrial fraction).[19]

Recently, LA function has been assessed by tissue Doppler imaging. The late diastolic velocity (Aa or A′) of the mitral annulus correlates with LA function[20] and decreases as atrial function deteriorates. Further, new echocardiographic techniques such as acoustic quantification are also being studied for the assessment of LA function.[21]

## DETERMINANTS OF LA SIZE

### Demographic and Anthropometric Determinants

*Age:* In healthy individuals, LA volume index is independent of age.[22] Previously observed changes in LA volume with aging are attributable to the pathophysiologic changes associated with normal aging process as opposed to the result of normal aging itself.[23]

*Gender:* LA size is larger in men than women, but this difference can be attributed to the variations in relative weight and body size.[13,22,23]

*Body Size:* Body size is the most important determinant of LA size, which increases with increasing body size. Therefore, LA size should be indexed to a measure of body size. Body surface area (BSA) is most commonly used for LA volume indexation; however, this might attenuate the adverse influence of obesity on LA size. A recent analysis by our group

showed that LA volume indexed to BSA may over- or underestimate the prevalence of LA enlargement in patients depending on their obesity status. However, LA volume indexed to height or height with allometric powers was unaffected by the level of obesity and appears to be preferable to indexing by BSA, which will need to be independently assessed in other populations.[24]

### Pathophysiologic Determinants

LA enlargement is mostly the result of pressure and/or volume overload. LA enlargement due to pressure overload is usually secondary to increased LA afterload in the presence of mitral stenosis or LV dysfunction. The relationship between LA enlargement and increased LV filling pressure has been shown in individuals with[25] and without[26] mitral valve disease. LA volume overload resulting from mitral valve regurgitation, arteriovenous fistula, left to right shunt, or high cardiac output state can also contribute to LA chamber remodeling.

### LA Volume as a Marker for Severity and Chronicity of Diastolic Dysfunction

During ventricular diastole, LA is directly exposed to LV pressures through the open mitral valve. With worsening LV compliance, LA pressure increases to maintain adequate LV filling, which results in LA enlargement. Therefore, LA volume may reflect the severity of diastolic dysfunction.[27] LA remodeling may also represent the chronicity of exposure to abnormal LV filling pressure.[27] Thus, LA volume as a reflection of severity and chronicity of diastolic dysfunction provides prognostic information incremental to that of diastolic function class determined by multiple load dependent Doppler parameters reflective of instantaneous LV diastolic function and filling pressures.[28] Therefore, LA volume has been termed ''glycosylated hemoglobin of diastolic dysfunction.'' Also, because of opposing effects of preload and compliance on transmitral velocities, the mitral inflow patterns may appear normal (pseudonormal) despite abnormal filling pressures.[29] In such situations, LA volume index provides the highest discriminative value in distinguishing between normal and pseudonormal transmitral filling patterns.[27] Therefore, assessment of parameters representing acute (Doppler echocardiographic parameters) and chronic (LA volume index) diastolic dysfunction provides the best prognostic power.

## CLINICAL IMPLICATIONS OF LA ENLARGEMENT

LA size has been established as a prognostic marker for adverse CV outcomes as well as overall outcomes.[30–42]

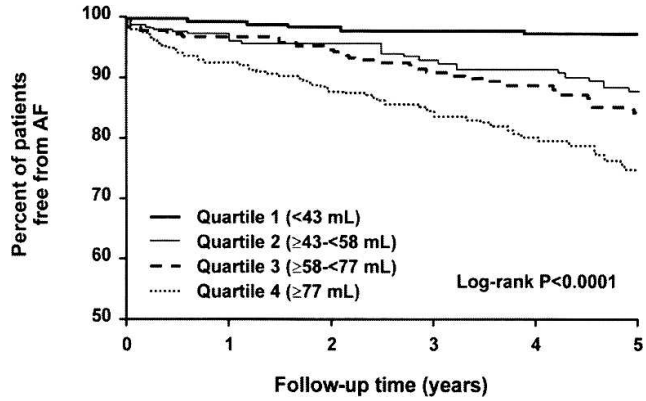


**Figure 2. Kaplan-Meier age-adjusted estimates of atrial fibrillation-free survival by indexed left atrial volume quartiles.** (Reproduced with permission from Tsang TS, et al. *Mayo Clin Proc.* 2001;76(5):467–475.[32])

### Atrial Fibrillation

Atrial fibrillation (AF) is a frequently encountered arrhythmia associated with increased morbidity and mortality. Several large population-based prospective studies have shown a strong association between M-mode anteroposterior LA diameter and the risk of new onset AF.[30,31] In the Framingham Heart Study, every 5-mm increase in LA diameter increased the development of AF by 39%,[30] while the Cardiovascular Health Study showed a four-fold increase in the risk of new AF with LA diameter >0.5 mm.[31] Similar to LA dimensions, studies using LA volume predicted AF in elderly patients (Figure 2)[32] as well as in patients with hypertrophic cardiomyopathy.[33] A recent prospective study found that not only the maximum LA volume (per tertile, hazard ratio: 1.8) but also the minimum LA volume (per tertile, hazard ratio: 2.4) were independent predictors of first AF or atrial flutter, incremental to clinical and other echocardiographic parameters of AF or atrial flutter prediction.[34] Furthermore, reduced LA reservoir functions, as estimated by total LA emptying fraction, have markedly increased the propensity for first AF or atrial flutter [hazard ratio: 5.4 (1.8–16), p=0.002], independent of clinical risk factors, LA volume, LV ejection fraction, and diastolic function grades.[35] Evidence from these studies indicates that LA volume encompasses information not captured by clinical data or one-dimensional M-mode assessment and thus represents a superior predictor of outcomes including AF.[32,33,36]

### Stroke

Stroke is the third leading cause of death and is associated with severe disability. The relationship between LA enlargement and stroke is complex. LA size has been shown to predict ischemic stroke in subjects without AF and mitral valve disease in the

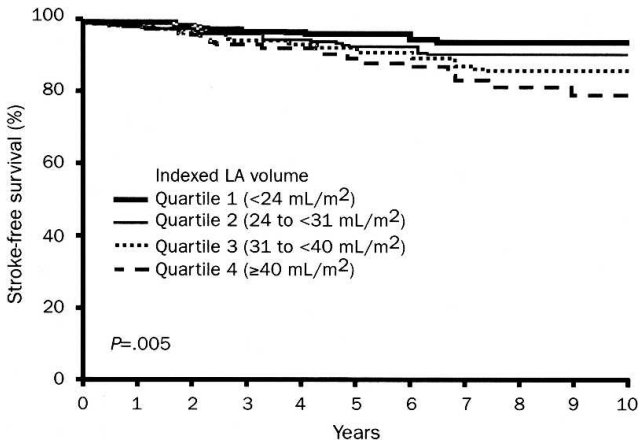


**Figure 3. Kaplan-Meier age-adjusted estimates of stroke-free survival by indexed left atrial volume quartiles.** (Reproduced with permission from Barnes ME, et al. *Mayo Clin Proc.* 2004;79(8):1008–1014.[41])

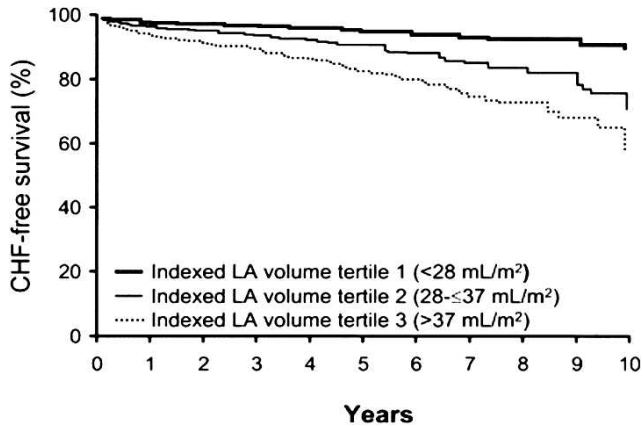


**Figure 4. Kaplan-Meier age-adjusted estimates of congestive heart failure-free survival by indexed left atrial volume tertiles.** (Reproduced with permission from Takemoto Y, et al. *Am J Cardiol.* 2005;96(6):832–836.[42])

Framingham Heart Study.[39] However, this association was partially mediated by LV mass that would in turn alter LV diastolic properties.[39] Similar findings were also observed in an ethnically diverse population in the Northern Manhattan Stroke Study.[40] Although the association between LA size and new onset AF and the association of AF with increased risk of stroke have been noted, the relationship between LA size and stroke does not appear to invariably involve AF. Recently, in elderly patients without AF at baseline, LA volume index ≥32 mL/m$^2$ was independently predictive of a first ischemic stroke (Figure 3).[41] This association persisted even after patients who developed AF during the follow-up were deleted from consideration.

## Heart Failure with Preserved Ejection Fraction

The LA volume is a sensitive barometer of LV filling pressure and reflects the burden of diastolic dysfunction in absence of severe valvular disease and AF.[27] Few recent studies have shown the utility of LA volume in predicting incident congestive heart failure (CHF) (Figure 4).[42,43] In one such study of older patients with preserved LV systolic function (ejection fraction ≥50%), LA volume ≥32 mL/m$^2$ was an independent predictor of first CHF.[42] Furthermore, from baseline to within 4 weeks of incident CHF, individuals with preserved ejection fraction had a mean increase of 8 mL/m$^2$ in LA volume, reflecting an additional burden of diastolic dysfunction in the preclinical phase of CHF. Prospective data from the Cardiovascular Health Study also showed an independent association of LA volume with incident and prevalent CHF.[43] This association of LA volume with prevalent CHF was similar for both systolic and diastolic HF. In a study of patients with suspected HF and normal LV systolic function, LA volume was a significant independent predictor of LV diastolic dysfunction as predicted by serum NTproBNP.[44] The recent update to the consensus statement by the Heart Failure and Echocardiography Associations of the European Society of Cardiology on the diagnosis of HF with normal LV ejection fraction considers LA volume index >40 mL/m$^2$ to provide sufficient evidence of diastolic dysfunction when the E/E′ ratio is non-conclusive (15>E/E′>8) or when NTproBNP is elevated. Similarly, LA volume index <29 mL/m$^2$ is proposed as a prerequisite to exclude HF with preserved systolic function.[45]

## CV and All-Cause Mortality

LA size has been shown to predict mortality, both CV as well as all-cause, in the general population.[46] However, in other population-based studies, the association of LA enlargement with mortality has been attenuated when diastolic function,[47] LV mass,[39] or LV hypertrophy[48] has been considered. In contrast, in recent trials such as the LIFE (Losartan Intervention for Endpoint reduction in hypertension) trial, LA diameter/height predicted the risk of CV events independent of other clinical risk factors in hypertensive patients with LV hypertrophy.[49] Similarly, in a very large study of patients referred for echocardiography, LA volume index predicted all-cause mortality independent of LV geometric patterns.[50] The prognostic implication of LA size has also been shown in high-risk subgroups, such as patients with acute myocardial infarction,[36,37] atrial arrhythmia,[51] LV dysfunction,[52] or dilated cardiomyopathy,[53] and patients undergoing valve replacement for aortic stenosis[54] and mitral regurgitations.[55]

## CONCLUSION

In light of current evidence, LA enlargement provides important clinical and prognostic informa-

tion. However, there is a need for a standardized method for evaluating LA size, and also the association between LA enlargement and CV outcomes needs to be further examined prospectively to define the generalized applicability of these findings to patient care. Nevertheless, current findings suggest that echocardiographically determined LA size may become an important clinical risk identifier in preclinical CV disease and should be assessed as a part of routine comprehensive echocardiography evaluation.

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