STATE-OF-THE-ART PAPER

Left Atrial Size
Physiologic Determinants and Clinical Applications

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Left atrial (LA) enlargement has been proposed as a barometer of diastolic burden and a predictor of common cardiovascular outcomes such as atrial fibrillation, stroke, congestive heart failure, and cardiovascular death. It has been shown that advancing age alone does not independently contribute to LA enlargement, and the impact of gender on LA volume can largely be accounted for by the differences in body surface area between men and women. Therefore, enlargement of the left atrium reflects remodeling associated with pathophysiologic processes. In this review, we discuss the normal size and phasic function of the left atrium. Further, we outline the clinically important aspects and pitfalls of evaluating LA size, and the methods for assessing LA function using echocardiography. Finally, we review the determinants of LA size and remodeling, and we describe the evidence regarding the prognostic value of LA size. The use of LA volume for risk stratification is an evolving science. More data are required with respect to the natural history of LA remodeling in disease, the degree of LA modifiability with therapy, and whether regression of LA size translates into improved cardiovascular outcomes. (J Am Coll Cardiol 2006;47:2357–63) © 2006 by the American College of Cardiology Foundation

There is strong evidence that left atrial (LA) enlargement, as determined by echocardiography, is a robust predictor of cardiovascular outcomes. Recently, it has been shown that LA volume provides a more accurate measure of LA size than conventional M-mode LA dimension (1). To optimize the use of LA volume for risk stratification, an understanding of the physiologic determinants of LA size and the methods for accurate quantitation is pivotal. Recent guidelines from the American Society of Echocardiography provide clarification as to which of the multiple methods for LA volume quantitation should be used in clinical practice (2). Such a standardized approach for LA volume assessment will be crucial for reproducible measures and communication of LA size between laboratories. Herein, we present an overview of LA size and function, and describe the physiologic determinants and clinical implications of LA enlargement.

LA PHASIC FUNCTION AND SIZE

The LA mechanical function can be described broadly by three phases within the cardiac cycle (3). First, during ventricular systole and isovolumic relaxation, the LA functions as a "reservoir" that receives blood from pulmonary venous return and stores energy in the form of pressure.

Second, during the early phase of ventricular diastole, the LA operates as a "conduit" for transfer of blood into the left ventricle (LV) after mitral valve opening via a pressure gradient, and through which blood flows passively from the pulmonary veins into the left ventricle during LV diastasis. Third, the "contractile" function of the LA normally serves to augment the LV stroke volume by approximately 20% (4). The relative contribution of this "booster pump" function becomes more dominant in the setting of LV dysfunction (5,6).

The size of the LA varies during the cardiac cycle (7–11). Generally, only maximum LA size is routinely measured in clinical practice. However, various LA volumes (8–11) can be used to describe LA phasic function:

1. Maximum LA volume occurs just before mitral valve opening.
2. Minimum LA volume occurs at mitral valve closure.
3. Total LA emptying volume is an estimate of reservoir volume, which is calculated as the difference between maximum and minimum LA volumes.
4. LA passive emptying volume is calculated as the difference between maximal LA volume and the LA volume preceding atrial contraction (at the onset of the P-wave on electrocardiography).
5. LA active emptying (contractile) volume is calculated as the difference between pre-atrial contraction LA volume and minimum LA volume.
6. LA (passive) conduit volume is calculated as the difference between LV stroke volume and the total LA emptying volume.

Abbreviations and Acronyms

2D	=	two-dimensional
3D	=	three-dimensional
AF	=	atrial fibrillation
CHF	=	congestive heart failure
LA	=	left atrial/atrium
LV	=	left ventricle/ventricular
PV_{ar}	=	pulmonary venous flow reversal during atrial systole
PV_d	=	pulmonary venous flow during early ventricular diastole
PV_{s1}	=	pulmonary venous flow during early ventricular systole
PV_{s2}	=	pulmonary venous flow during late ventricular systole

The relative contribution of LA phasic function to LV filling is dependent upon the LV diastolic properties (12) and therefore varies with age (8). In subjects with normal diastolic function, the relative contribution of the reservoir, conduit, and contractile function of the LA to the filling of the LV is approximately 40%, 35%, and 25%, respectively (12). With abnormal LV relaxation, the relative contribution of LA reservoir and contractile function increases and conduit function decreases. However, as LV filling pressure progressively increases with advancing diastolic dysfunction, the LA serves predominantly as a conduit (12).

ASSESSMENT OF LA SIZE AND FUNCTION

Two-dimensional and Doppler methods have been used increasingly for the assessment of LA size and function, respectively.

LA size assessment. Measurement of anteroposterior LA linear dimension by M-mode echocardiography (13,14) is simple and convenient but not reliably accurate, given that the LA is not a symmetrically shaped three-dimensional (3D) structure (15). Furthermore, because LA enlargement may not occur in a uniform fashion (16), one-dimensional assessment is likely to be an insensitive assessment of any change in LA size. In contrast to LA dimension, LA volume by two-dimensional (2D) or 3D echocardiography provides a more accurate and reproducible estimate of LA size, when compared with reference standards such as magnetic resonance imaging (MRI) and cine computerized tomography (CT) (17–20), and has a stronger association with cardiovascular outcomes (1,21,22). Accordingly, the American Society of Echocardiography has recommended quantification of LA size by biplane 2D echocardiography using either the method of discs (by Simpson's rule) or the area-length method (2). Although we have routinely used the area-length method in our laboratory, we have found that the biplane Simpson's method is comparable in accuracy and reproducibility. Critical elements and common pitfalls for accurate and reproducible measurement of bi-

Table 1. Critical Elements and Common Pitfalls for Accurate Measurement and Interpretation of Maximum LA Volume*

Step	Common Limitations/Errors	Suggestions
A. Optimize LA image quality	Atria are located in the far field of the apical views. Reduction of lateral resolution may result in apparently thicker LA walls.	Not improved by modifying the gain settings: Increase in gain will further reduce LA lumen size Decrease in gain may lead to image "drop out" and difficulties in planimetry of LA area Use high resolution sample box to increase pixel density and facilitate accurate tracing of the endocardial border Capture at least five beats for each cine loop to maximize likelihood of obtaining adequate image quality
B. Obtain maximal LA size	LA is foreshortened	Modify transducer angulation or location (place the transducer one intercostal space lower) until LA image is optimized and not foreshortened If discrepancy in the two lengths measured from the orthogonal planes is >5 mm, acquisition should be repeated until the discrepancy is reduced
C. Timing of maximum LA size	Correct frame for measurement is not selected	Choose frame just before mitral valve opening
D. LA area planimetry	LA border is inconsistently defined	Consistently adhere to convention: Inferior LA border—plane of mitral annulus (not the tip of leaflets) Exclude atrial appendage and confluences of pulmonary veins
E. Long-axis LA length	LA long axis is inconsistently delineated	Consistently adhere to convention: Inferior margin—midpoint of mitral annulus plane Superior (posterior) margin—midpoint of posterior LA wall
F. Interpretation	Qualitative categorization of LA size	LA volume indexed to body surface area is optimally interpreted as a continuous variable (using a reference point of 22 ± 5 ml/m² as "normal")

*Also see the Appendix.
LA = left atrial.

plane LA volume assessment are detailed in the Appendix and outlined in Table 1.

Echocardiographic methods systematically underestimate LA volume when compared with CT (23) or MRI quantitation (19), which in turn underestimates true LA size (11). More recently, magnetic electroanatomic mapping has also been used for assessment of LA volume (24). However, because of its portability and safety, echocardiographic assessment of LA volume is preferable to other imaging methods in clinical practice.

LA volume reference limits. Reference values for 2D echocardiographic maximum LA volumes have been estimated using data collected on persons free of cardiovascular disease, although few samples have been population based (21,25). Published reference values for maximum and minimum LA volumes are 22 ± 6 ml/m^2 (26) and 9 ± 4 ml/m^2 (27), respectively. In a study of LA function, mean total LA emptying volume was 13.5 ± 4.3 ml/m^2 (representing $37 \pm 13\%$ of LV stroke volume), fractional emptying of the LA was $65 \pm 9\%$, and conduit volume was 23 ± 8 ml/m^2 (28).

Assessment of LA function by echocardiography. Pulsed-wave Doppler evaluation of transmitral and pulmonary venous blood flow velocity can be used for assessment of LA function, in addition to its widespread use for the evaluation of LV diastolic function and filling pressure (29–31). The normal pulmonary venous flow pattern reflects flow from the pulmonary veins to the LA during early ventricular systole (PV_{s1}; seen distinctly in about 30% of transthoracic echocardiography studies [32]), late ventricular systole and isovolumic relaxation (PV_{s2}), early ventricular diastole (PV_d), and reversal of flow from the left atrium to pulmonary veins during atrial systole (PV_{ar}). Apart from flow in late ventricular systole (reflected by PV_{s2}), which represents propagation of the right ventricular pressure pulse through the pulmonary circulation (33), blood flow in the pulmonary veins is determined by events that regulate phasic LA pressure (34). The magnitude and velocity-time integral of the PV_s waves reflect LA reservoir function and are determined by LV systolic function and LA relaxation (PV_{s1}), LA compliance (PV_{s1} and PV_{s2}), and right ventricular stroke volume (PV_{s2}) (33). Peak velocity and velocity-time integral of PV_d is an index of LA conduit function (35) and is dependent on factors that influence LA afterload: LV relaxation and early filling (12) and mechanical obstruction from the mitral valve apparatus (36). During LA contraction, blood is ejected from the LA into the LV and the pulmonary veins. Thus, assessment of transmitral (peak A-wave velocity, A-wave velocity-time integral, and atrial filling fraction) (6,37) and pulmonary venous blood flow (PV_{ar}) (38) provides additive information for the evaluation of LA booster pump function. More recently, global and regional atrial contractile function has been evaluated with pulse wave and color tissue Doppler imaging (8), but the incremental clinical utility of this assessment remains to be determined. Further, new echocardiographic techniques, such as with automated border detection using acoustic

quantification, are being developed to facilitate evaluation of LA size and function (8).

DETERMINANTS OF LA SIZE AND REMODELING

Demographic and anthropometric influences. Body size is a major determinant of LA size. To adjust for this influence, LA size should be indexed to a measure of body size, most commonly to body surface area (21,25). It remains to be clarified if this approach attenuates obesity-related variations in LA volume, which may be prognostically significant (39). Gender differences in LA size are nearly completely accounted for by variation in body size (8,21,40,41). In persons free of cardiovascular disease, indexed LA volume is independent of age from childhood onward (42). Indeed, age-related LA enlargement is a reflection of the pathophysiologic perturbations that often accompany advancing age rather than a consequence of chronologic aging (9). The relation of LA size to race or ethnicity has not been sufficiently studied.

Atrial structural remodeling. Many conditions are associated with LA remodeling and dilatation. The atria will enlarge in response to two broad conditions: pressure and volume overload. The relationship between increased LA size and increased filling pressures has been validated against invasive measures in subjects with (43,44) and without (30,45) mitral valve disease. Left atrial enlargement due to pressure overload is usually secondary to increased LA afterload, in the setting of mitral valve disease or LV dysfunction. Case reports have suggested that LA dilatation can also occur in response to pressure overload resulting from fibrosis and/or calcification of the LA. This condition, known as "stiff LA syndrome" (46,47), causes a reduction of LA compliance, a marked increase in LA and pulmonary pressures, and right heart failure. Chronic volume overload associated with conditions such as valvular regurgitation, arteriovenous fistulas, and high output states including chronic anemia and athletic heart (48,49), can also contribute to generalized chamber enlargement. Both volume and pressure overload can increase atrial size. However, pressure overload is uniformly accompanied by abnormal myocyte relaxation, while volume overload is characteristically associated with normal myocardial relaxation physiology.

LA volume as an expression of LV filling pressures. In subjects without primary atrial pathology or congenital heart or mitral valve disease, increased LA volume usually reflects elevated ventricular filling pressures. During ventricular diastole, the LA is exposed to the pressures of the LV. With increased stiffness or noncompliance of the LV, LA pressure rises to maintain adequate LV filling (50), and the increased atrial wall tension leads to chamber dilatation and stretch of the atrial myocardium. Thus, LA volume increases with severity of diastolic dysfunction (22,51). The structural changes of the LA may express the chronicity of exposure to abnormal filling pressures (22,45) and provide predictive information beyond that of diastolic function grade (52), which is determined from evaluating multiple load-dependent

Table 2. Maximum Left Atrial Volume as a Predictor of Cardiovascular Outcomes

Author (Year Published) (Ref. #)	Study Design	Study Population	Sample Size (Age, yrs)	Study Outcome	Volume Method	Discriminatory Threshold (ml/m²)	Risk Ratio
Tsang et al. (2001) (62)	Retrospective cohort	Clinic based	1,655 (75 ± 7)	AF	A-L	Quartiles	—
Tsang et al. (2002) (63)	Retrospective cohort	Clinic based	840 (75 ± 7)	AF	A-L	Tertiles	—
Rossi et al. (2002) (64)	Prospective cohort	DCM patients	337 (60 ± 13)	Death or heart Tx	A-L	>68.5	3.8
Tsang et al. (2003) (65)	Retrospective cohort	Clinic based	1,160 (75 ± 7)	Combined events*	A-L	≥32	—
Moller et al. (2003) (66)	Retrospective cohort	AMI patients	314 (32–94)	Death	A-L	>32	6.1
Tsang et al. (2004) (67)	Retrospective cohort	Mild LVDD patients	569 (76 ± 7)	AF, CHF	A-L	>27	—
Tani et al. (2004) (68)	Case control	HCM patients	141 (61 ± 13)	AF	A-L	≥34	—
Losi et al. (2004) (69)	Prospective cohort	HCM patients	150 (4–83)	AF	A-L	>27	—
Barnes et al. (2004) (70)	Retrospective cohort	Clinic based	1,554 (75 ± 7)	Ischemic stroke	A-L	≥32	1.6
Beinart et al. (2004) (71)	Prospective cohort	AMI patients	395 (62 ± 12)	Death	MOD	>32	2.2
Sabharwal et al. (2004) (72)	Prospective cohort	ICM patients	109 (63 ± 9)	Death	PE	≥60	—
Takemoto et al. (2005) (73)	Retrospective cohort	Clinic based	1,495 (75 ± 7)	CHF	A-L	≥32	2.0
Gottdiener et al. (2006) (74)	Prospective cohort	Community based	851 (78 ± 6)	CHF	PE	Quartiles	—
Tsang et al. (2006) (75)	Prospective cohort	Clinic based	423 (71 ± 8)	Combined events*	A-L	34–<40 ≥40	3.2 6.6

All discriminatory limits have been indexed to body surface area. *Atrial fibrillation (AF), myocardial infarction, congestive heart failure (CHF), coronary revascularization, transient ischemic attack, stroke, or cardiovascular death.

A-L = area length method (biplane unless specified); AMI = acute myocardial infarction; BSA = body surface area; DCM = dilated cardiomyopathy; LVDD = left ventricular diastolic dysfunction; HCM = hypertrophic cardiomyopathy; ICM = ischemic cardiomyopathy; MOD = method of discs by Simpson's rule; PE = prolate-ellipsoid method; Tx = transplantation.

parameters and therefore reflective of the instantaneous LV diastolic function and filling pressures. In this way, analogous to the relationship between hemoglobin A_{1C} and random glucose levels, LA volume reflects an average effect of LV filling pressures over time, rather than an instantaneous measurement at the time of study (53). Thus, Doppler and tissue Doppler assessment of instantaneous filling pressure is better suited for monitoring hemodynamic status in the short term, whereas LA volume is useful for monitoring long-term hemodynamic control.

Left atrial size as an expression of diastolic function and filling pressures has not been fully evaluated in specific conditions. Most studies of LA size and outcomes have excluded patients with atrial fibrillation (AF). The relationship between AF and LA volume is complex (54). It has been difficult to establish the causal relationship between AF and LA structural remodeling. In patients with AF and cardiac disease, structural LA alterations may be related to the underlying cardiac pathophysiology rather than solely the arrhythmia itself (55,56). Experimental animal studies have documented that sustained atrial tachyarrhythmias induce electrical, contractile and structural remodeling (57). In some cases, it appears that LA structural remodeling may be related to high ventricular rate and increased ventricular filling pressures rather than to the atrial tachyarrhythmia itself (58,59). However, in other individuals, the size of the LA varies widely for given LV relaxation and filling properties, suggesting a hysteresis between LA size and filling pressures. Few studies have assessed the impact of sustained AF on atrial structure in patients with lone AF (60).

LA SIZE FOR THE PREDICTION OF CARDIOVASCULAR OUTCOMES

There is considerable data confirming the relationship between increased LA size, principally maximal but also minimal (30,61), and the development of adverse cardiovascular outcomes in subjects without a history of AF or significant valvular disease (62–75) (Table 2).

AF. Atrial fibrillation is the most common of the serious cardiac arrhythmias and is associated with increased morbidity and mortality in the community. Prospective data from the large population-based studies have established a relationship between M-mode anteroposterior LA diameter and the risk of developing AF (76,77). In the Framingham study, a 5-mm incremental increase in anteroposterior LA diameter was associated with a 39% increased risk for subsequent development of AF (76). In the Cardiovascular Health Study, subjects in sinus rhythm with an anteroposterior LA diameter >5.0 cm had approximately four times the risk of developing AF during the subsequent period of surveillance (77). More recently, LA volume has been shown to predict AF in patients with cardiomyopathy (68,69) and first-diagnosed nonvalvular AF in a random sample of elderly Olmsted County residents who had undergone investigation with a clinically indicated echocardiogram (62,63). The relationship between LA volume and LA dimension was nonlinear (68), and it has been confirmed that LA volume represented a superior measure over LA diameter for predicting outcomes including AF (62,68,75) and

provided prognostic information that was incremental to clinical risk factors (62).

Stroke. Stroke is the leading cause of severe long-term disability and the third largest contributor to mortality in the U.S. (78). Despite the strong association between AF and ischemic stroke, 85% of strokes occur in patients who are in apparent sinus rhythm (78). In the general population, LA size has been determined to be a predictor of stroke and death (79). Increased LA volume has also been shown to predict the onset of first stroke in clinic-based elderly persons who were in sinus rhythm and did not have a history of ischemic neurologic events, AF, or valvular heart disease (70). Even after censoring for the development of documented AF, an indexed LA volume ≥ 32 ml/m^2 was associated with an increased stroke risk (hazard ratio [HR] 1.67, 95% confidence interval [CI] 1.08 to 2.58) over 4.3 $\pm$ 2.7 years, independent of age and other clinical risk factors for cerebrovascular disease.

Heart failure. As previously discussed, LA volume is a barometer of LV filling pressure and reflects the burden of diastolic dysfunction in subjects without AF or significant valvular disease (22). Elevation of filling pressure is uniformly found in the presence of symptomatic congestive heart failure (CHF). Because the majority of individuals in the community with LV dysfunction (systolic or "isolated" diastolic) are in a preclinical phase of the disease (80), methods to quantify the risk of progression to symptomatic heart failure would be clinically useful. Evidence for a prognostic role for LA volume to predict incident CHF is emerging (73,74). In a large prospective, population-based study, subjects with incident CHF during follow-up had slightly higher baseline LA linear diameters (39 mm vs. 37 mm for women [p < 0.01], 41 mm vs. 39 mm for men [p < 0.01]) (81). In a study of older adults referred for echocardiography, LA volume ≥ 32 ml/m^2 was associated with increased incidence of CHF, independent of age, myocardial infarction, diabetes mellitus, hypertension, LV hypertrophy, and mitral inflow velocities (HR 1.97, 95% CI 1.4 to 2.7) (73). Furthermore, in subjects with an LV ejection fraction $\geq 50\%$ at baseline and within four weeks of incident CHF, there was an increase of 8 ml/m^2 in LA volume from baseline to CHF diagnosis, reflecting the added burden of diastolic dysfunction during the period of transition from preclinical to clinical status.

Mortality. The relationship between LA size and death has been demonstrated in high-risk groups, such as patients with dilated cardiomyopathy (64), LV dysfunction (82), atrial arrhythmias (83), acute myocardial infarction (66,71), and patients undergoing valve replacement for aortic stenosis (84) and mitral regurgitation (85). The LA diameter has also been shown to independently predict death in the general population (81). However, in other population-based studies, the relationship between LA size and death has been attenuated when LV mass (79), LV hypertrophy (86), or diastolic function (51) has been considered. Thus, owing to the intimate relationship between

LA volume, LV mass/hypertrophy, and diastolic dysfunction, the incremental value of each parameter for the prediction of death is diminished when considering the others.

Although a dilated LA is associated with a number of adverse outcomes, there is increasing evidence suggesting that LA size is potentially modifiable with medical therapy (87–96), but whether LA size reduction translates to improved outcomes remains to be established.

CONCLUSIONS

Left atrial enlargement carries important clinical and prognostic implications. Left atrial volume is superior to LA diameter as a measure of LA size, and should be incorporated into routine clinical evaluation. Future studies are warranted to further our understanding of the natural history of LA remodeling, the extent of reversibility of LA enlargement with medical therapy, and the impact of such changes on outcomes. The utility of LA volume and function for monitoring cardiovascular risk and for guiding therapy is an evolving science and may prove to have a very important public health impact.

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APPENDIX

For the measurement of LA volume by echocardiography, please see the online version of this article.