EDITORIAL

Left Atrium and Cardiovascular Risk: Does Functionality Matter More Than Size?

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The left atrium (LA) is often regarded as a biomarker of cardiovascular risk. It serves several important functions: it modulates left ventricular filling and cardiovascular performance by functioning as a reservoir for pulmonary venous return during ventricular systole; it is a conduit for pulmonary venous return during early ventricular diastole; and it functions as a booster pump that augments ventricular filling during late ventricular diastole.[1] It is highly dynamic and demonstrates structural, functional, and electrical remodeling in a time-dependent manner in response to various pathophysiological insults. The hallmark of structural remodeling is atrial dilatation and is frequently accompanied by increased interstitial fibrosis with cardiac structural alterations.[2] Functional impairment may occur with or without alteration in LA size. Remodeling that occurs in the initial phase is often reversible,[3] in contrast to remodeling that occurs with ongoing "stressors" over longer duration.[4] These maladaptive changes have a strong association with a wide array of conditions, including heart failure,[4] hypertension,[5] myocardial ischemia,[6] obesity,[7] and obstructive sleep apnea.[8] In tandem with structural change, electrophysiologic abnormalities develop, including global and regional conduction slowing and changes in refractoriness predisposing to onset of atrial arrhythmias and ultimately atrial fibrillation (AF).

Atrial size and function can be assessed with echocardiography, cardiac computed tomography, and cardiac magnetic resonance, but because of its safety, relative low cost, and universal availability, echocardiography is the most widely applied first-line modality. Many of the earlier measures of atrial function were only measurable during sinus rhythm, making comparisons in subjects with AF challenging. These measures include the following: (1) peak "A" wave velocity and velocity time integral of transmitral flow in late diastole; (2) estimation of the fractional contribution of atrial contraction to total mitral inflow; and (3) the use of Doppler tissue imaging as a global measure of atrial function. Recent advances in 2- and 3-dimensional echocardiography, including in tissue Doppler imaging, and speckle tracking for strain analysis[9] have allowed evaluation of atrial function during AF. These varying parameters have distinct strengths and weaknesses and are complementary in differing clinical scenarios. The LA function index (LAFI) uses volumetric measurement of the LA and is a composite rhythm-independent measure of LA function. It is a ratio that incorporates analogues of cardiac output, atrial reservoir function, and LA size and is calculated as follows: LAFI=(LA emptying fraction×velocity time integral across the left ventricular outflow tract)/largest LA volume measure in ventricular systole indexed to body surface area.[10] Thus, LAFI increases proportionally to LA reservoir function and stroke volume, but it is inversely proportional to LA size.

It has become increasingly recognized that structural and functional remodeling are important factors that determine cardiovascular prognosis and risk stratification. Several studies have demonstrated this association in different population subsets. In a single-center study[11] that included ambulatory patients with heart failure and reduced ejection fraction (<40%) who were clinically stable and optimally treated, LAFI was a predictor of long-term survival. Patients in the lower LAFI quartile had more severe heart failure symptoms, renal function, and left ventricular systolic function. Subgroup analysis by heart rhythm (sinus rhythm versus AF) revealed that this remained consistent in both subgroups. LAFI was also noted to be a predictor of heart failure hospitalization in another population-based cohort study with stable coronary artery disease and preserved baseline ejection fraction (≥50%).[12] Besides functional remodeling, LA enlargement alone estimated by LA volume indexed to body

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surface area has also been demonstrated to predict adverse cardiovascular events in patients with stable coronary artery disease,[13] valvular heart disease,[14] and dilated cardiomyopathy.[15]

The association between echocardiographic parameters of atrial remodeling and AF has also been extensively documented. In a case-control cohort, structural and functional LA remodeling assessed by echocardiogram were independently and strongly associated with paroxysmal AF.[16] Assessment of LA size and function has also been useful to predict the success of restoring sinus rhythm in patients with AF after either direct-current cardioversion[17] or catheter ablation.[18] Electrophysiologic mapping studies have demonstrated that these echocardiographic markers of remodeling are associated with both electrical conduction slowing and regional atrial fibrosis; both are also strongly linked to progression of AF.[19] More recently, a retrospective cohort study of patients with AF showed that more severe LA fibrosis, as detected by late gadolinium enhancement on cardiovascular magnetic resonance imaging, was associated with increased major cardiovascular and cerebrovascular event risk, driven primarily by increased risk of stroke or transient ischemic attack.[20]

The study by Sardana et al,[21] in this issue of *Journal of the American Heart Association* (*JAHA*), provides new insights into the predictive power of LA remodeling in incident AF and cardiovascular disease (CVD). In a prospective analysis of 1786 participants from a longitudinal community-based cohort, the authors investigated how LAFI, as an echocardiographic marker of structural and functional remodeling, may better characterize adverse LA remodeling and predict incident AF and CVD than existing measures. The CHARGE-AF (Cohorts for Heart and Aging Research in Genomic Epidemiology-AF) and the 10-year Framingham Heart Study CVD risk models were used to determine its association with AF and CVD, respectively. There were 3 key observations made over a median follow-up of 8.3 years (range, 7.5–9.1 years). First, LAFI was associated with incident AF (hazard ratio, 3.83) and CVD (hazard ratio, 2.20), an association that persisted after adjustment for both clinical prediction scores and for echocardiographic parameters associated with AF and CVD. More important, the association remained strong, even in patients with normal LA volume. In the current study, the authors also confirmed prior studies demonstrating that the anteroposterior LA diameter was associated with incident AF and CVD events. The LA diameter was measurable in most participants with echocardiographic images suboptimal for the measurement of LA volumes. However, addition of LAFI, LA diameter, or indexed maximum LA volume to prediction models for AF or CVD did not significantly improve model discrimination for either outcome. Thus, although LAFI may represent an important echocardiographic marker of adverse cardiovascular risk, even in the presence of normal LA size, it does not seem to add further discrimination to already robust clinical prediction models.

The current study reiterates the clinical importance of assessing LA remodeling in cardiovascular prognostication. The study supports the use of LAFI, which provides a composite measure of LA structure and function. In comparison, simpler echocardiographic measures, such as LA volume indexed to body surface area, currently recommended for risk stratification by consensus guidelines, provide a more limited structural evaluation only. Apart from being rhythm independent, LAFI adjusts LA function for LA size and attempts to isolate atrial remodeling from ventricular systolic function. Future large prospective studies will be needed to determine whether LAFI is the ideal tool for evaluation of atrial remodeling, together with incident AF and cardiovascular risk. The current study emphasizes that in left atrial prediction of cardiovascular risk, function may matter more than size alone.

Disclosures

None.

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