

Left Atrial Volumes in Health and Disease Measured Using Cardiac Magnetic Resonance.

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“It is not the size of a man, but the size of his heart that matters.” – Evander Holyfield

The left atrium in health and disease

The left atrium (LA) plays an important mechanical role in cardiac performance. There are three discrete phasic functions within the cardiac cycle: first, the LA acts as a reservoir for storing pulmonary venous return during left ventricular (LV) contraction; second, it acts as a conduit as blood is passively transferred into the LV; third, active LA contraction in LV end-diastole contributes significantly to LV filling. It is also responsible for secreting natriuretic peptides in response to stretch, thus helping to mediate fluid and haemodynamic homeostasis.

Given these various and important functions, it is little surprise that disturbances of LA morphology are associated with important cardiovascular comorbidities such as stroke¹, heart failure², atrial fibrillation (AF)³, and even premature mortality⁴. Overall LA size has been the most widely investigated atrial characteristic, and has been found to be consistently increased in association with these and other cardiovascular complications. Given the enormous and increasing combined public health impact of these diseases, there is significant clinical interest in LA imaging as a potential biomarker to not only identify individuals at increased risk (suggested by the presence of LA remodelling), but also to guide potential treatments and assess the therapeutic response - i.e. “reverse” LA remodelling⁵.

Assessment of left atrial size

The traditional metric of LA size has been the anteroposterior LA diameter in ventricular end-systole (i.e. maximal atrial dimension within the cardiac cycle), measured from a parasternal long axis M-mode echocardiographic view. This approach has advantages, given the widespread availability of echocardiography and the ease and reproducibility of this particular measurement. However, the LA is a morphologically complex chamber, and overall volume is more accurately estimated using the biplane area-length method which combines LA areas and lengths measured on orthogonal (4- and 2-chamber) 2-dimensional imaging⁶. Crucially, this approach is more sensitive to the degree of LA enlargement in disease states, where LA length as well as diameter changes⁶.

Cardiovascular magnetic resonance imaging (CMR) has now become the gold standard method for assessment of cardiac volumes and function⁷. While CMR offers unlimited imaging planes and hence the ability to obtain a stack of short axis images through the LA, the same biplane area-length method validated in echocardiography is a more rapid alternative, which remains accurate and reproducible⁸. While normal values for LA size by CMR have been reported in healthy volunteers^{7,9}, previous studies have lacked power to closely investigate the relationships between LA size and clinical characteristics.

Population-based assessment of left atrial volumes

In this issue of *Circulation: Cardiovascular Imaging*, Zemrak et al. present the results of assessment of LA volume in 2576 participants in the Multi-Ethnic Study of Atherosclerosis (MESA)¹⁰. Over 5000 individuals, from four ethnic groups and aged between 45-84, first underwent CMR imaging in MESA in 2000-2002; these individuals were selected at baseline to be free of “end-organ” cardiovascular disease such as myocardial infarction, stroke or heart failure (but importantly not necessarily free of risk factors, such as hypertension or diabetes). Of these, 3016 underwent repeat imaging using modern steady-state free precession CMR cine imaging in 2010-2011. It is only the left atrial volumes determined from this latter examination that are now reported, after exclusion of 416 participants in whom left atrial image quality was insufficient and of a further 24 with incomplete cardiovascular risk factor data. The authors also selected a sub-group of 283 individuals with normal body mass index and no risk factors or cardiovascular disease at the time of the latter CMR examination, for the purpose of determining “normal” LA volume. The biplane area-length method was used to determine maximal atrial volume (i.e. in LV end-systole), with internal validation against the multi-slice short axis method in a subgroup of participants confirming excellent correlation between methods (ICC 0.97).

The mean age of the included participants was 69 years, with almost equal numbers of men and women. The majority were Caucasian (~42%), while black African-American, Hispanic and Chinese American individuals accounted for 25%, 21% and 12% of the study population, respectively, making this a representative population sample of the USA. There was a high prevalence of cardiovascular risk factors including hypertension (~57%), diabetes (~17%), overweight/obesity (mean BMI 28 ± 5 kg/m²) and current or former smoking (~54%). Given these demographics, it is somewhat surprising that the prevalence of AF was only 1.2% (compared to ~3.6% in a similarly-aged representative sample of Medicare beneficiaries¹¹).

Zemrak et al. mainly report LA volume indexed to body surface area (i.e. LA volume index). The main findings from the adjusted multivariate linear regression models were positive associations between LA volume index and age, female gender, Hispanic ethnicity, and LV end-diastolic volume index, while Chinese American ethnicity was negatively associated with LA volume index. LV end-systolic volume index and mass index were not included in the multivariate model to avoid collinearity, but separate models substituting these variables individually for LV end-diastolic volume index showed that they too were independently associated with LA volume index. Finally, analysis of the “normal” individuals provides upper limits (mean+2SD) for LA volume index in healthy people of this age: ~56ml/m² in females and ~54ml/m² in males.

The authors are to be congratulated for this large and systematic assessment of atrial volume. In particular, the internal validation against the short axis method and careful assessment of inter- and intra-observer variability reassure us that the findings are robust. However, this work also has some limitations: as valve disease (such as mitral regurgitation) was not assessed on the available CMR images, and because echocardiography was not undertaken within MESA, the impact of valve disease on LA volume could not be addressed in this study. Furthermore, the LA minimum volume (i.e. in LV end-diastole) was not calculated or reported in this manuscript, but has been reported recently in this Journal using a subgroup of the MESA data set¹² and in a further prior MESA publication¹³. This is pertinent as LA minimum volume is more strongly associated than LA maximum

volume with development of both atrial arrhythmias¹⁴ and subclinical cerebrovascular disease¹⁵. Additionally, the present study did not report the LA volumes in the included individuals at the baseline (2000-2002) MESA CMR examination. Such an analysis would yield interesting and rich data on change in LA volumes over time; it is possible that the association between demographics/risk factors and LA enlargement per unit time may be more clinically relevant than the association with a point estimate of LA volume.

Clinical implications of identified associations with left atrial volumes

The findings of the study by Zemrak et al.¹⁰ are largely in line with our current understanding of atrial pathophysiology, and in particular investigations of AF, the disease most closely linked to LA size. LA remodelling (including dilatation) is almost universally seen in AF, despite AF being a heterogeneous condition with complex underlying pathophysiology¹⁶ that includes associations with systemic and LV disease¹⁷. Chronic atrial stretch is thought to be mechanistically important and linked to fibrosis, cellular hypertrophy and inflammation, leading to conduction slowing and heterogeneity as well as increased stability of re-entrant circuits, thus contributing to the substrate for the arrhythmia¹⁶. Epidemiological studies in AF have demonstrated that its incidence and prevalence are closely related to increasing age¹⁸, with lower prevalence in China and other Asian countries¹⁸. Similarly, the association between AF and other cardiovascular conditions such as hypertension, diastolic dysfunction and heart failure is well-recognised^{16, 19}.

One more unexpected, and potentially clinically important, finding from the present study is that male gender is associated with smaller indexed LA volume in a multivariable regression model. The direction of change is similar for non-indexed LA volume in a multivariable model that includes LV end-diastolic volume in the “normal” individuals without risk factors (see Supplementary Table S4¹⁰), suggesting that the gender variation in atrial size remains in apparently healthy individuals and when accounting for cardiac size (rather than overall body size). These findings are in apparent conflict with the 60% higher age-adjusted prevalence of AF in men compared to women¹⁸. Integration of these disparate observations suggests that there may be potential differences in the underlying mechanisms for AF between the genders, which would merit further investigation. The prospective UK Biobank cohort study, in which 100,000 individuals will undergo CMR²⁰ and serial follow-up for development of cardiovascular disease (including AF) is likely to shed further light in this regard.

Future directions: going beyond atrial volumes

Atrial size has traditionally been the most accessible metric of atrial remodelling and is established as a biomarker that predicts future cardiovascular events. However, more advanced imaging techniques are now available that will potentially refine the phenotyping of atrial structure and function. For example, LA longitudinal strain derived from speckle tracking echocardiography may have value in estimating left ventricular end-diastolic pressure, and can be combined with tissue Doppler imaging to determine LA stiffness (which may be related to LA fibrosis)²¹.

CMR offers the exciting opportunity to go a step further, by directly imaging cardiac tissue characteristics such as with late gadolinium enhancement (LGE) for the detection of focal scar. Some centres have significant experience in the detection and quantification of left atrial structural remodelling using atrial LGE, particularly in relation to AF²². Yet, LGE imaging of the thin LA wall challenges the spatial resolution of conventional CMR imaging, is prone to artefact and noise, and is difficult to quantitatively analyse²³. For these reasons, it remains to be reliably reproduced in many centres (including our own). Meanwhile, parametric mapping (including T1-mapping) may be more sensitive to diffuse changes within cardiac tissue (such as diffuse myocardial fibrosis). These techniques have been widely applied to characterisation of the left ventricle, and there is growing interest in harnessing them for evaluation of LA tissue²⁴.

Finally, we may need to go beyond the atrium to investigate the pathophysiology of AF. Our recent data suggest that AF may be the consequence of an occult cardiomyopathy²⁵. This paradigm implies that atrial dilatation and remodelling do not occur in isolation, but rather as part of a more global disease process. Indeed, a randomised clinical trial has shown that holistic treatment with weight loss and intensive risk factor management is effective in reducing AF symptom burden and severity, and also results in beneficial cardiac remodelling²⁶.

Conclusion

The present study by Zemrak et al. makes a significant contribution to our knowledge of the factors affecting LA size in health and disease¹⁰. Yet we will have to delve much deeper if we are to truly understand the interplay between ageing and cardiovascular risk factors, atrial morphology and function, and complex multisystem diseases such as heart failure or AF.

Conflict of Interest Disclosures

None.

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