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EDITORIAL COMMENT

The Importance of Left Atrial Function in Ischemic Cardiomyopathy*

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Patients with ischemic cardiomyopathy (ICM) face a significantly increased risk of severe morbidity and mortality, underscoring the need for accurate risk stratification and tailored therapeutic interventions. While the role of left ventricular (LV) function has firmly established as the primary indicator of outcomes in ICM, the role of the function of other cardiac chambers, and particularly the right ventricle and the left atria (LA) have been longtime overlooked.[1] Indeed, the LA contributes significantly to LV filling, and LA dysfunction is closely associated with LV diastolic dysfunction which is a well-known independent predictor of all-cause mortality in many diseases.[2] Comprehensive imaging techniques, like cardiovascular magnetic resonance (CMR), provide a wealth of additional information on these chambers, paving the way for identification of novel and precise risk markers. Regarding this topic, left atrial function evaluation by CMR is becoming of great interest as a possible prognostic marker in heart failure and ICM, with accumulating evidence supporting this investigation line.

Advancing in this innovative area of research, the work conducted by Anthony et al[3] in this journal adds another piece to this puzzle, focusing on the role of left atrial ejection fraction (LAEF) measured by CMR as a prognostic predictor in patients with advanced ICM. The authors conducted an observational retrospective study, that included 782 patients with ischemic disease and LV dysfunction (<40% ejection fraction), referred for CMR. Notably, 8% of the patients were excluded due to suboptimal image quality of the left atrium. The study's primary endpoint was a composite of all-cause mortality and cardiac transplantation, aiming to establish the relationship between LAEF and these major outcomes. At a median follow-up of 4.8 years, there were 416 primary outcome events, mainly driven by all-cause mortality.

Remarkably, a decrease in LAEF was independently associated with increased incidence of mortality or the need for transplantation in patients with ICM, HR 0.24 (95% CI: 0.12-0.48), highlighting a significant and continuous influence of LAEF on adverse outcomes within this cohort. Incomplete revascularization, absence of implantable cardioverter-defibrillator, and combined high myocardial infarct size (MIS) and significant mitral regurgitation (MR) were also associated with increased risk of death or heart transplant. The study also investigated the relationship between LAEF (using values of 50% and 20% to represent normal and significantly decreased levels), MIS, and functional MR fraction, in order to demonstrate the impact of these factors on patient outcomes. It found that patients with higher LAEF and larger infarct sizes have worse outcomes, particularly those with an MIS >30% and an MR fraction above 35%, who have a HR of 3.2 (95% CI: 1.73-5.93), thus emphasizing the value of LAEF as a tool for further stratifying risk.

This study by Anthony et al[3] in this issue of *JACC: Advances* marks a significant milestone, and the authors should be congratulated. Undoubtedly, it stands out by the size of the patient population, extensive duration of follow-up and high event rate. This robust design facilitated the thorough examination of the supplementary contribution of LA function

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in multivariable analysis, against other well-established outcome predictors within this specific population. The key finding of the study was to demonstrate the independent association between reduced LAEF and worse outcomes in ICM patients, even when adjusted for traditional risk factors. Why is this important? Because it enhances the risk stratification in patients with ICM, a group highly susceptible to cardiovascular events. We often concentrate on the question of "Which medication to use," but equally important is "When is the right time to use it?." The effort to identify high-risk subgroups assists us in this regard, pinpointing patients who are at risk and who might benefit from starting medication earlier. Furthermore, it emphasizes the vital role of CMR in providing a more comprehensive assessment of heart function. In fact, Alfuhied et al[4] evaluated test-retest reproducibility and observer variability of CMR-derived LA volumes and EF, concluding that its reproducibility was very good. All these findings advocate for a wider adoption of CMR evaluation of LA function in ICM patients.

However, it is essential to mention certain limitations to this study. First, this is a retrospective, single-center study, which might have influence upon the generalizability of these findings. Also, the exclusion of 8% of the cohort due to suboptimal image quality flags a potential issue in widespread CMR application for LAEF evaluation. In light of the established correlation between LAEF and atrial fibrillation, it would have been particularly insightful to disentangle the influence of both processes. A comprehensive investigation into the specific involvement of the LA in distinct patient cohorts would have enhanced the study's analytical depth. Also, the current examination exclusively focused on LAEF, without delving into more sophisticated assessments of LA function, such as the evaluation of LA strains. LA strains are indeed a metrics allowing a finder understanding of the LA physiology. Specifically, they enable a nuanced exploration of the LA function as a reservoir, depending on its relaxation, a conduit, primarily contingent upon the suction from the LV, and its booster function, contingent upon its intrinsic contractility, an aspect notably absent in atrial fibrillation. CMR LA strains have indeed been shown to be highly predictive in patients after acute infarcts[5,6] and/or with dilated cardiomyopathy.[7] The study's depth could also have been enriched by delving into a more comprehensive understanding of diastolic function. This could have been achieved through the inclusion of echocardiographic parameters such as mitral E/A pulsed-wave Doppler and tissue Doppler Imaging annular measurements, alongside estimates of pulmonary artery pressures. Moreover, the incorporation of additional metrics such as LV global longitudinal strain and gadolinium-extracellular volume fraction might have provided a more nuanced assessment, offering insights into the stiffness of the LV. This broader spectrum of measurements would have afforded a more holistic perspective on the diastolic aspects of cardiac function, enhancing the study's overall interpretative capacity.

This study definitely sets the stage for further investigations. The imperative next step involves the initiation of prospective, multicenter trials, a pursuit that is indispensable for validating the current findings and unraveling the broader implications and relevance of LAEF and LA strains within varied patient cohorts. Of particular significance is the endeavor to ascertain whether these findings can be extrapolated to echocardiography, leveraging LA strain measurements. It would also be particularly important if the finding could be generalized to echocardiography, being more widely accessible than CMR, by means of LA strain measurements. Therefore, establishing the generalizability of these findings to echocardiographic methodologies would significantly enhance their practicality and applicability in clinical settings.

In conclusion, the study's pivotal finding that LAEF is a significant prognostic marker in ICM opens new lines of research for patient risk assessment and management. This insight not only enhances our current understanding of atrial-ventricular interaction but also paves the way for future research to explore new prognostic markers and refine cardiac care strategies for this high-risk group.

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