Changes in the Left Atrium and Heart Failure: Chicken or Egg?

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The left atrium (LA) serves distinct roles to maintain cardiac physiology. It works as a reservoir to receive and store blood from the pulmonary veins, it passively allows blood to enter the left ventricle (LV), and contributes with final LV filling through active contraction1. As such, measurement of LA size and function provides important insights into cardiac hemodynamics as well as clinically relevant information across a series of clinical conditions, including patients with heart failure (HF)2.

With the rise in HF incidence and prevalence world-wide3, there is a bound incentive to identify
individuals at-risk of developing this condition, as it comes with high morbidity and mortality. Identifying high risk subjects could allow for preventive measures, potentially through more aggressive risk factor management.

In the current issue of the journal, Lim et al. reports on important information on this topic from the Multi-Ethnic Study of Atherosclerosis (MESA) study, a prospective, community-based cohort study. The authors investigated how changes in LA measures were related to incident HF based on cardiac magnetic resonance (CMR) imaging. Lim et al. included 2470 participants free of cardiovascular disease at baseline, who underwent serial CMR imaging (median time of 9.4 years). Of these, 73 developed incident HF during a median follow-up of 7.1 years. Based on an LVEF cut-off of 50%, 39 of these events were considered HF with preserved ejection fraction (HFpEF) and 34 were HF with reduced ejection fraction (HFrEF).

The authors observed that all investigated LA measures were independently associated with any incident HF event, with delta values ($\Delta$) in minimal LA volume (LAVmin) showing highest discriminative values by C-statistics, whereas $\Delta$LA strain and $\Delta$LA pre-atrial contraction volume showed highest discriminative values for predicting HFpEF and HFrEF, respectively. Remodeling of the LA and deterioration of LA function has been linked to an increased risk of HF in community-based cohort studies, but these have mainly been based on cross-sectional studies. The current study is therefore a welcome and important addition to the literature. The study has several strengths, including equal gender distribution as well as multiethnic representation, that make it more generalizable than prior studies. The main finding suggesting that $\Delta$LAVmin was most predictive of any HF events corroborates previous findings we have made based on longitudinal echocardiographic data in the Copenhagen City Heart Study. It is, however, interesting to note that the authors observed differential prognostic value of LA measurements when considering HF phenotypes. Clinically, it may be argued that prediction of any HF is the most relevant goal, however, a stratified approach may inform on the underlying pathophysiology driving HFpEF and HFrEF, respectively. There are, however, some limitations that cloud the interpretation of these findings. Overall, relatively few events were observed, particularly within each subgroup of HF phenotype. This implies that some of the regression models may have been overfitted, such that some parameters may not have shown an independent association to the specific outcomes. In example, $\Delta$LA pre-atrial contraction volume was not associated with HFpEF after multivariable adjustments, which could reflect this issue. For the HFrEF outcome, the authors argue that LV passive filling has a greater impact on the development of HFrEF since $\Delta$LA pre-atrial contraction volume showed highest predictive value. This notion could have been substantiated further by including...
additional measures of atrial function, i.e. conduit strain, contraction strain, passive LAEF, and active LAEF. For the HFpEF outcome, the authors correctly state that LA strain reflects both reservoir function and compliance. They emphasize that their findings suggest that LA dysfunction may be a primary process in the development of HFpEF. However, it is well-known that the LV descent during systole is a major determinant of LA strain. Even though studies have suggested a potential value of LA strain beyond global longitudinal strain (GLS), it is unclear whether this is also the case in the present study since neither GLS nor LVEF were included and accounted for. In fact, cross-sectional findings from the MESA study have previously shown that LA strain is closely related to LV fibrosis, further emphasizing the issue of potential confounding effects from LV function in the aspect of HFpEF.

Finally, it is also worth mentioning that while certain LA measures yielded higher discrimination than others, the absolute differences in C-statistics were marginal. It is therefore debatable how superior each of the specific parameters were in terms of predicting HF compared to the other LA measures. It is also important to note that only patients who were alive for follow-up exams were included in the study, introducing an element of survival bias that may also impact the findings.

A final aspect that deserves mentioning is the issue of causality. The authors state that “This suggests that change in LA parameters are situated along the causal chain and may confer and individual an increased risk of incident HF event development.”. Even though the authors have made a tremendous effort in linking LA measures to HF by considering longitudinal assessment of the LA, it is impossible to infer any type of causality based on these findings. Several other mechanisms may be at play. For example, findings from both the MESA study and the Copenhagen City Heart Study have linked changes in LA measures to an increased risk of atrial fibrillation (AF), that could promote the development of HF. Even though the authors accounted for AF diagnosed at follow-up, asymptomatic AF could still have been present. A high burden of device-detected AF has been linked to an increased risk of HF in the ASSERT study, and findings from the LOOP study have shown that an increasing burden of device-detected AF leads to deterioration in GLS, which could confer such an increased risk of HF just as it would likely lead to a deterioration in LA strain. This implies that is not possible to tease out the cause and effect of undetected AF and LA dysfunction in relation to HF. Finally, even though the MESA study performed rigorous data collection with patient contact every 9 months and review of medical records, subjects may still have had recall bias in this process. They could also have had contact with their general practitioner at any point during follow-up with symptoms suggestive of congestion that were relieved with diuretics or other treatment. As such, HF could have been developing clinically without resulting in admission or workup at an outpatient clinic. Such issues apply to any longitudinal study.
Since we cannot gain full details about what is happening throughout the follow-up period, the chain of causation cannot be established. In other words: it cannot be clarified with certainty whether HF may have preceded changes in LA measures or vice versa. Once again, we are faced with the chicken or egg conundrum.

Data availability statement: No new data is presented in this article.

References


