Longitudinal Strain in Heart Failure with Preserved Ejection Fraction:

Is There a Role for Prognostication?

Running title: Mentz et al.; Strain in Heart Failure with Preserved EF

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Heart failure with preserved ejection fraction (HFpEF) represents approximately 50% of the overall heart failure (HF) population\(^1\), yet relatively few prognostic markers are used in routine clinical practice. Clinicians commonly assess symptom severity, prior HF hospitalizations, natriuretic peptide levels and comorbidity burden to characterize disease trajectory. Furthermore, without disease-modifying agents, the management of HFpEF is largely limited to optimization of volume status and comorbid conditions\(^2\). In contrast, for patients with HF with reduced EF (HFrEF), clinicians incorporate an array of data from clinical evaluation and diagnostic testing to risk-stratify patients, individualize guideline-based medication regimens and determine optimal timing for implantable devices and advanced therapies. For instance, thresholds for echocardiographic and exercise testing parameters (e.g., EF and maximal oxygen consumption) are central components of the decision-making process for defibrillator implantation and advanced therapies such as ventricular assist devices\(^2\). An equivalent prognostic marker to EF has not been identified for HFpEF patients despite the similarly high event rate compared to HFrEF cohorts\(^3,4\).

Given that HFpEF patients have normal systolic function as quantified by EF, measures of diastolic dysfunction on echocardiography (e.g., myocardial tissue relaxation and ventricular inflow patterns) have been used to characterize disease severity\(^5\). However, these parameters have modest sensitivity and specificity\(^6,7\). An alternative diagnostic measure that captures the underlying myocardial abnormality in HFpEF with superior fidelity would help with both diagnostic and prognostic dilemmas. For instance, such a test could help determine if progressive dyspnea was due to worsening HF or whether another disease process (e.g., lung disease) should be investigated. Moreover, if the parameter was shown to be modifiable with therapy and modulation translated into improved clinical outcomes, this would change the landscape of
HFpEF care and clinical research. Such a biomarker could inform the understanding of HFpEF pathophysiology and potentially serve as a surrogate endpoint to facilitate drug development. It is in this context that Shah AM et al in this issue of Circulation investigated the prognostic utility of left ventricular (LV) longitudinal systolic strain (LS) in HFpEF and whether this parameter improved with spironolactone therapy.

Myocardial deformation imaging using two-dimensional (2D) speckle-tracking strain echocardiography (STE) is the 2D tracking of unique speckle patterns created by the constructive and destructive interference of ultrasound beams within tissue. These speckles are tracked on a frame-by-frame basis and the accuracy of speckle-tracking has been validated against sonomicrometry and tagged cardiac magnetic resonance imaging. Strain reflects the global deformation of ventricular myocardium during the cardiac cycle, is typically measured at peak systole (i.e., aortic valve closure) for systolic strain, and can be determined in the longitudinal, radial, and circumferential planes. Longitudinal systolic strain is more reproducible and may be less susceptible to technical factors that limit EF assessments by conventional 2D echocardiography (2DE).

Measurement of LS by 2D-STE has also emerged as a more sensitive index of myocardial systolic performance than EF. Measurements of EF by 2DE principally assess load dependent changes in LV cavity size that may not reflect actual myocardial systolic function. In comparison, LS can detect subtle systolic dysfunction despite preserved global EF in HFpEF, cardiac amyloidosis, and patients receiving cardiotoxic chemotherapy. Longitudinal strain also appears to provide superior prognostic information to EF in patients with diverse cardiac conditions; a recent meta-analysis showed that LS independently predicted mortality better than EF in 5,721 patients with HFrEF, myocardial infarction, valvular heart
disease, and cardiac amyloidosis. However, prior to the current publication, limited data were available regarding the prognostic utility in HFpEF patients.

Shah AM et al investigated LS in 447 patients with LVEF ≥45% in the echocardiography substudy of the Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial. Abnormal LS as defined by an absolute value <15.8% was associated with a more than 2-fold increase in the composite endpoint of cardiovascular (CV) death, HF hospitalization or aborted cardiac arrest. This association persisted following adjustment for clinical risk factors and conventional echocardiographic measures including EF, LV size and diastolic dysfunction. Similar findings were observed when the cohort was restricted to those with EF ≥55% or in a subgroup with adjustment for natriuretic peptide level. However, when the incremental value of impaired LS for risk prediction was assessed through additional statistical techniques, LS provided marginal additive utility beyond conventional measures for predicting the composite outcome. On the other hand, LS data yielded modest incremental value for the prediction of the CV death component. In a small subgroup of 131 patients with serial LS assessment, treatment with spironolactone as compared with placebo was associated with a trend toward improvement in LS over 12-18 months in the Americas.

These data from a fairly large cohort of well-characterized HFpEF patients provide important insights into the potential role for routine use of strain imaging in prognostication. One takeaway message is that impaired LS, as specifically defined and assessed in the context of the TOPCAT trial dataset and core laboratory, was an independent prognostic marker in HFpEF with greatest value in predicting CV death. The strengths of the study include the robust methodology involving strain evaluation in a core laboratory, blinded endpoint adjudication and rigorous statistical techniques to assess implications of missing data and specifically evaluate the
incremental value of LS beyond conventional risk factors. Moreover, the exploratory analysis of the change in LS with randomized therapy provides important hypothesis-generating data with respect to potential benefits with spironolactone in HFrEF.

However, several considerations need to be highlighted when interpreting these data. First, these data are from a clinical trial dataset which has important differences from the broader population of HFrEF patients. For instance, despite TOPCAT’s entry criteria requiring age \( \geq 50 \) years, the trial population was significantly younger than HFrEF patients in community cohorts\(^1\). Moreover, the analysis cohort in the present study was a subgroup of a trial subgroup. The TOPCAT echocardiography substudy included 27% of the overall study population and adequate strain data were available in 14%. The echocardiography substudy population had notable differences from the overall trial cohort and additional differences were seen when comparing those with adequate quality strain data versus those without. Furthermore, while having an expert core laboratory using vendor-independent speckle-tracking software previously demonstrated to have good reproducibility for longitudinal strain\(^2\) is a strength for assessing efficacy under optimal conditions, the effectiveness in the real-world is unknown. Currently, there are inherent limitations to the widespread use of strain echocardiography, including dependency on high quality images, variability related to different vendor acquisition and analysis platforms as well as uncertainty regarding normal cut-off values and inter-institutional reproducibility. These observations do not necessarily discredit the findings, but rather, should highlight some degree of uncertainty with respect to generalizability.

In addition, the models for the analysis of the incremental value of LS over conventional clinical and echocardiographic variables demonstrated an unexpected finding. Previous analyses suggest that clinical variables are usually better able to predict fatal events (i.e., higher c-index)
than rehospitalization events in HF populations. For instance, in the OPTIMIZE-HF risk model of acute HF patients, the c-index for the multivariable model of death was 0.74 compared to 0.64 for the composite of death or hospitalization\textsuperscript{20}. It is interesting to note that the predictive capacity of the clinical and echocardiographic parameters used in the present analysis was greater for HF hospitalization than for CV death (0.74 vs. 0.66, respectively, for the models without LS). The specific reasons for these findings are uncertain but suggest that future work is needed to assess the added value of LS for the prediction of clinical events.

In the end, the question lies in how these results should be incorporated into our subsequent clinical behavior. These data suggest that there is a strong association between abnormal LS and worse outcomes, particularly CV death, but that the incremental value beyond conventional risk predictors is modest. Nonetheless, we view these data from the perspective of the glass half full. Given the limited resources available to objectively characterize HFpEF disease severity, LS has the potential to help inform clinical practice. These patients will likely have one (or more) echocardiograms performed serially and the added time, expense, and expertise to assess LS may be balanced by the incremental knowledge gained. However, these results should be validated in independent datasets prior to broad application.

In addition, several questions warrant further study. First, can strain interpretation be similarly performed amongst the broad population of clinical providers? Second, is a threshold value of 15.8\% optimal for sensitivity and specificity of LS in HFpEF? Finally, the finding that LS can improve with spironolactone therapy is intriguing and requires further study. Despite the clearly articulated limitations of the subgroup analyses, these findings provide mechanistic data to support the observation of reduced HF hospitalizations with spironolactone in HFpEF patients enrolled in the Americas. For HFpEF patients, these new observations add insights into the
biologic basis for improved outcomes and support initiating spironolactone with the usual
appropriate monitoring. In addition, these mechanistic observations lay the foundation for future
work to validate the potential role of LS as a surrogate marker for investigation of novel drugs to
treat HFpEF.

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