Heart Failure With Preserved Ejection Fraction

Do You Know Your Left Atrial Strain?

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ymptomatic heart failure, despite preserved left ventricular (LV) ejection fraction, is a well-recognized phenomenon. This manifestation of diastolic dysfunction is associated with increased morbidity and mortality and can be attributed to a variety of pathogeneses, including diabetes mellitus, hypertension, infiltrative processes, and obesity.1–5 Unlike in systolic heart failure, where LV ejection fraction readily stratifies disease severity, accurate diagnosis and grading of heart failure with preserved ejection fraction (HFpEF) can be a challenging. Without an equivalent, single, noninvasive diagnostic tool in HFpEF, we must instead rely on a myriad of measures to establish diagnosis and severity. This is best illustrated by the current European and American guidelines, which incorporate ≤8 separate imaging indices into their diagnostic tool in HFpEF, we must instead rely on a myriad of measures to establish diagnosis and severity. This is best illustrated by the current European and American guidelines, which incorporate ≤8 separate imaging indices into their recommended protocols for diagnosis and classification of diastolic dysfunction.6,7 Although, new guidelines from the American Society of Echocardiography and the European Association of Cardiovascular Imaging will attempt to simplify assessment of diastolic dysfunction with the use of 4 key variables, such as mitral annular early diastolic (e') velocities, average E/e' ratio, indexed left atrial (LA) volume, and peak tricuspid regurgitant velocity (personal communication, A.L. Klein, MD, unpublished data, 2016).

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strain analysis was triggered off the ECG QRS complex. This differs from previously described methodology, where the ECG p wave of atrial contraction was used as the point of zero reference. They also only performed LA strain analysis on standard 4- and 2-chamber apical views, rather than the 3-chamber long-axis view technique previously described. These methodological differences could potentially affect the resultant LA strain values obtained, the generalizability of their results and the ability to compare these data to other study populations. Nonetheless, their strain imaging technique appeared relatively robust overall, with acceptable reproducibility on intra- and interobserver variability analysis. Unsurprisingly, their symptomatic cohort had a high proportion of moderate or severe diastolic dysfunction (75%) and increased wall thickness (81%). Although LVEF was preserved, other markers of systolic function including tissue Doppler and strain were reduced in a majority of subjects, suggesting that there actually was a degree of underlying systolic dysfunction in this cohort. Right ventricular strain was also reduced in nearly half of the study population, highlighting the often global nature of the underlying pathogenesis. These LV parameters and other related measures including increased LV mass index and E′/e⁄ ratio were also associated with adverse outcomes, although LA strain was a more powerful predictor overall. LA size was increased in two thirds of subjects, although may be overestimated as their definition of enlargement (>28 mL/m²) is lower than the new guideline recommended threshold of 34 mL/m². This discrepancy may help to explain why LA volume index was not associated with adverse outcomes, although it also suggests that once the LA is enlarged, size becomes less relevant than LA function to outcome in HFpEF. Perhaps our long-standing focus on LA enlargement and its relationship to diastolic classification has been somewhat misguided? Recent data highlighting the disparity between indexed LA volume measurements by echocardiogram compared with cardiac magnetic resonance imaging further highlights some inherent issues with this volumetric technique.

Overall, reservoir strain seemed the most predictive of the prespecified study end points and demonstrated an independent association with the composite outcome of cardiovascular hospitalization or death, which was noted in 37% of subjects after a median follow-up of 13.8 months. The relatively high occurrence of their primary composite end point, after such a limited follow-up period, supports that HFpEF is not a benign entity and suggests that this population may be relatively high risk for all-cause mortality because of other factors. This is supported by other notable associates of adverse outcomes including age, poorer functional class, chronic kidney disease, heart failure therapy, elevated B-type natriuretic peptide, and anemia among others. On bivariate correlation, impaired LA strain was unsurprisingly associated with multiple factors representing diastolic and systolic dysfunction, including increased B-type natriuretic peptide, LV mass, and E′/e⁄ ratio, along with reduced exercise capacity (oxygen consumption [VO2 max]). Although perhaps unexpectedly, in the limited invasive cohort (n=177), reservoir LA strain demonstrated an inverse association with several factors including pulmonary vascular resistance, but not pulmonary capillary wedge pressure. Although chronic pulmonary congestion in HFpEF may ultimately result in elevated pulmonary vascular resistance, it seems unusual that pulmonary capillary wedge pressure would not be affected by increased LV diastolic pressures. This also goes against other previous observational data, which highlights an inverse relationship between LA strain and pulmonary capillary wedge pressure. The nonrandomized nature of the right-heart catheterization subgroup detracts from our ability to interpret these data or apply it to the broader HFpEF population and further investigation is required.

One consistent limitation of LA strain has always been LA wall thinness, with resultant wall drop out and poor tissue tracking, especially in the setting of LA enlargement. This again seems to have been problematic in this study, illustrated by the 55 eligible subjects (15%) who were excluded because of poor image quality. This study also further demonstrated that generation of LA strain curves requires manual tracing and adjustment of LA borders and strain curve thickness. This lack of technique automaticity detracts from its ability to be widely adopted in clinical practice. This partly relates to time pressures associated with such a labor intensive activity, but also the apparent reliance on experts to perform, adjust, and interpret the generated curves. Although performance of different LA strain techniques has previously shown comparable results, it cannot be incorporated into formal guideline recommendations until it can be broadly adopted in clinical echocardiographic laboratories within reasonable time frames. Although strain analysis in this study was performed using commercially available TomTec strain analysis software, this program has been less used for the measurement of LA strain than others, including EchoPAC (GE Vingmed) and vector velocity imaging (Siemens), so that the normal value of LA strain for this vendor–neutral software remains unknown. To circumvent this issue, the authors instead adopted published EchoPAC normal values that may have impacted diagnostic accuracy for identification of subjects with abnormal LA strain. Unfortunately, the authors did not include normal control subjects to internally validate parameters of normal strain using the TomTec strain analysis program. Finally, performance of multiple correlations and incorporating multiple variables (including several LA covariates) within regression models increases the propensity for a type 1 error and must be acknowledged.

Perhaps questionably, subjects in atrial fibrillation were included in the study design and accounted for ≈1 quarter of participants. Although measurements were repeated in triplicate for these patients to account for beat to beat variability, LA strain results were lower overall in atrial fibrillation. One postulates that this could simply relate to the absence of LA contraction, rather than true diastolic dysfunction, but requires further clarification. It also seems that subjects in sinus rhythm with a history of paroxysmal atrial fibrillation, direct current cardioversion, LA ablation, or pulmonary vein isolation were also indiscriminately included in the study. This is relevant because subjects with reduced LA strain undergoing catheter ablation are less likely to maintain sinus rhythm long term. Hence, all these factors may have detrimentally influenced LA strain results because of impaired LA compliance and contraction related to atrial stunning or fibrosis, independent of diastolic function. In practice, this can often be confirmed on spectral Doppler echocardiography, where
there is an absence of late diastolic mitral inflow because of absent LA contraction post cardioversion and ablation, despite the restoration of sinus rhythm.

The article by Freed et al\textsuperscript{14} illustrates the importance of LA function to outcome in the population with HFpEF and provides a sound argument for more routine assessment of LA strain within this cohort.\textsuperscript{14} Its superior performance over more routine measures such as LA size and biventricular strain in predicting adverse outcomes (including future cardiovascular hospitalizations and death) is an important finding, but the reason for superiority over ventricular strain remains unclear. The most conclusive results were evident for reservoir strain, suggestive that impaired LA compliance and relaxation have the greatest physiological impact on diastolic function. Establishing the underlying pathophysiology was beyond the scope of this article, but remains an important goal for future research. Diffuse, reactive LA fibrosis related to remodeling from chronically elevated afterload in diastolic dysfunction is a likely culprit but needs to be verified histologically.

In addition to providing an alternative methodological marker of prognosis in HFpEF, LA strain shows potential for serial measurement of disease severity or treatment response in HFpEF, thereby reducing the need to repeat the broad battery of diastolic parameters on every review. The authors mention the potential for novel shunt and assist devices in this population; however, quantitative measurement of treatment response to current simple therapeutics such as diuretics may also prove incredibly helpful. Although performance of LA strain seems to be feasible and reproducible based on this study’s inter- and intraobserver statistics, technique standardization and vendor–neutral normal values need to be better established and validated before LA strain can be adopted into routine clinical practice and guideline recommendations.

Disclosures
None.

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