Published in final edited form as:

Echocardiography. 2020 November ; 37(11): 1936–1943. doi:10.1111/echo.14764.

Cardiac mechanics in heart failure with preserved ejection fraction

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is a complex clinical entity associated with significant morbidity and mortality. Common comorbidities including hypertension, coronary artery disease, diabetes, chronic kidney disease, obesity, and increasing age predispose to preclinical diastolic dysfunction that often progresses to frank HFpEF. Clinical HFpEF is typically associated with some degree of diastolic dysfunction, but can occur in the absence of many conventional diastolic dysfunction indices. The exact biologic links between risk factors, structural changes, and clinical manifestations are not clearly apparent. Innovative approaches including deformation imaging have enabled deeper understanding of HFpEF cardiac mechanics beyond conventional metrics. Furthermore, predictive analytics through data-driven platforms have allowed for a deeper understanding of HFpEF phenotypes. This review focuses on the changes in cardiac mechanics that occur through preclinical myocardial dysfunction to clinically apparent HFpEF.

Keywords

diastolic dysfunction; HFpEF; machine learning; precision phenotyping

1 | INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is a complex clinical entity associated with significant morbidity and mortality. HFpEF is responsible for approximately half of all heart failure hospitalizations, with mean survival similar to those with heart failure with reduced ejection fraction.¹ HFpEF typically begins with risk factor exposure, which promotes abnormal cardiac mechanics and preclinical myocardial dysfunction. Preclinical diastolic dysfunction is present in approximately ¼ of the adult population.² A significant proportion of patients with diastolic dysfunction go on to develop frank clinical heart failure.

The exact biologic links responsible for diastolic dysfunction and heart failure are not clearly apparent, but can be attributed to a complex inter-play of various pathological

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CONFLICT OF INTEREST

PPS is a consultant for HeartSciences and Ultrasonics. CMB is a principal investigator for an AstraZeneca heart failure with preserved ejection fraction trial. KS has no conflicts.

conditions on background aging.³ Until recently, myocardial determinants of HFpEF were thought primarily related to impairments in left ventricular relaxation and chamber stiffness. However, contemporary studies recognize the contribution of subtle left and right ventricular systolic dysfunction, as well as the impact of left atrial function and pericardial compliance. Furthermore, myocardial dysfunction may initially occur only during exercise and the static resting evaluation may not fully characterize potential dynamic changes. Therefore, the assessment of cardiac mechanics during rest and exercise plays an important role in diagnosis and prognostication.⁴ This review focuses on the changes in cardiac mechanics that occur through the spectrum of preclinical myocardial dysfunction into clinically apparent HFpEF.

2 | LEFT VENTRICULAR MECHANICS

Each myocardial layer contributes to longitudinal, circumferential, and radial deformation. Longitudinal deformation is largely dependent on a well-functioning subendocardial fiber layer, while circumferential deformation of the left ventricle (LV) is predominately dependent on the subepicardial fiber layer.⁵ LV shearing forces occur within the three-dimensional myofiber orientation causing the largest shear force in the circumferential-longitudinal plane referred to as LV twist or torsional deformation. The rotation of LV base and apex in opposite directions, combined with twist shearing forces, is responsible for translating a mere 15%–20% maximal myocyte length shortening into an ultimate LV cavity volume reduction in over half. These same shear forces are responsible for untwisting during diastolic recoil. Left ventricular diastolic untwisting releases stored mechanical energy and creates a suction effect that facilitates movement of blood from the left atrium (LA) to the LV.

The predominant myocardial mechanics of HFpEF or restrictive cardiomyopathies involve subendocardial fiber dysfunction leading to decrements in longitudinal strain. Epicardial layer-derived circumferential strain and torsional shear forces remain relatively preserved or even increased to supranormal values early in the disease course.⁶ These compensatory circumferential and twist mechanics allow for the preservation of ejection fraction. On the other hand, constrictive pericarditis, a common HFpEF mimic, leads to a reciprocal situation of decreased circumferential and torsion forces, while longitudinal forces are preserved.⁷ These cardiac mechanics can serve as an adjunct to traditional echocardiographic signs differentiating features of constrictive vs restrictive physiology, as clinical presentation may be similar between disease states.

2.1 | Preclinical Myocardial Dysfunction

Traditional imaging biomarkers may be normal in early subclinical disease; however, reduced global longitudinal strain (GLS) related to subendocardial dysfunction is common (Figure 1). The prevalence of reduced GLS in asymptomatic type 2 diabetes mellitus has been reported to range from 37% to 54%.⁸ Impaired longitudinal strain may be present prior to the onset of LV remodeling and hypertrophy.⁹ Furthermore, reduced longitudinal strain may exist despite normal or near normal conventional Doppler and tissue Doppler-derived parameters of diastolic function¹⁰ (Figure 2). Compensatory subepicardial

hypertrophy may develop in an effort to reduce subendocardial wall stress and preserve ejection fraction.¹¹ Despite mild, resting impairment in longitudinal mechanics, those with preclinical myocardial dysfunction typically augment longitudinal strain to near normal values during exercise.¹² Complex interactions between protracted risk factor exposure and progressive structural changes influence the progression from the asymptomatic phase to symptomatic heart failure. High-risk structural findings in asymptomatic patients at elevated risk of progression to symptomatic disease include elevated E/e' , left ventricular hypertrophy (LVH), and abnormal GLS.¹²

2.2 | Clinical Heart Failure

Left ventricular cardiac mechanics associated with symptomatic heart failure are complex and often counterintuitive. Several investigators have shown that impaired longitudinal strain is a frequent finding in symptomatic HFpEF patients (Figure 2) and predictive of poor outcomes.^{13,14} Although a deterioration in longitudinal mechanics is common, global circumferential strain (GCS), LV twist, and twist/untwist rates may remain normal or even increase to supranormal values⁶ early in the disease course (Figure 1). This allows for the preservation of the ejection fraction via compensatory contributions from the subepicardial layer to circumferential and LV twist deformation. If subepicardial dysfunction is present and compensation is not possible, ejection fraction falls.¹⁵ Circumferential and twist deformation may remain normal or increased early in the disease course. However, time to peak twist and untwist is often prolonged and signals subtle impairments of systolic and diastolic function.¹⁶ Advanced HFpEF is characterized by a progressive deterioration of twist/untwist mechanics, as well as circumferential, radial, and longitudinal deformation.^{17,18}

Resting deformation can be used to predict invasive hemodynamics. In HFpEF patients, the ratio of mitral E to global longitudinal strain rate in isovolumic relaxation can predict left ventricular filling pressure.¹⁹ Furthermore, the ratio of resting global circumferential strain to global longitudinal strain can serve as potential predictor of a pathologic rise in pulmonary capillary wedge pressure during exercise.²⁰

Exercise imaging for diastolic function and cardiac mechanical assessment can aid tremendously in the initial HFpEF diagnostic workup. Recent guidelines recommend functional exercise echocardiographic stress testing in patients at intermediate likelihood of HFpEF following an initial morphofunctional assessment.²¹ Despite impaired resting longitudinal deformation, those with preclinical disease can augment longitudinal mechanics during exertion to a greater extent than those who have progressed to symptomatic heart failure. This in part explains the initial onset of exertional symptoms alone in patients transitioning from preclinical disease into frank clinical heart failure.²² Furthermore, impaired GLS during exercise has been independently associated with an increased occurrence of all-cause mortality and HF hospitalizations.²³

3 | LEFT ATRIAL MECHANICS

Left atrial (LA) enlargement has long been recognized as a marker of increased cardiovascular risk.²⁴ However, impaired LA phasic function evident by reduced strain

occurs prior to LA enlargement and may be an early marker of risk.²⁵ Thin atrial walls challenge deformation analysis; however, a growing body of evidence utilizing LA strain is accumulating and recent guidelines for standardization of LA deformation have been published.²⁶

The LA functions as a reservoir for pulmonary venous return during ventricular systole, as a conduit during early ventricular filling, and as a contractile booster pump that contributes to late ventricular filling. Atrioventricular deformation is closely inter-related and governed by the concepts of atrioventricular coupling. Reservoir function is dependent on both atrial volume and compliance, as well as LV systolic longitudinal annular excursion. Conduit function is dependent on the atrioventricular pressure gradient created during LV diastolic recoil. Atrial contractile function is dependent on both intrinsic pump function and late diastolic ventricular afterload.

3.1 | Preclinical Myocardial Dysfunction

Preclinical LA dysfunction is characterized by reduced reservoir and conduit function, while atrial contractile function remains normal²⁷ or even increased²⁸ (Figure 3). Early in the disease spectrum, compensatory enhanced LA contractile function is necessary for enhanced late LV filling. LA deformation abnormalities occur prior to clear LA anatomic remodeling. Impaired reservoir phasic performance may occur in the absence of diastolic dysfunction or ventricular remodeling.²⁵ In patients with normal LA size, impaired LA reservoir function is associated with an increased risk of future heart failure hospitalization.²⁹ In at-risk hypertensive patients, decreased LA contractile function is strongly predictive of future adverse cardiac events and death.³⁰ Furthermore, hypertension risk mitigation strategies including renin-angiotensin-aldosterone system inhibitor institution lead to improvements in LA strain.³¹

3.2 | Clinical Heart Failure

A growing body of literature supports the pivotal role of LA functional failure leading to pulmonary congestion and symptom onset. Specifically, atrial contractile failure to compensate for reservoir and/or conduit dysfunction may lead to overt clinical heart failure³² (Figure 3). Atrial fibrillation leading to failure of contractile compensation may be a large determinant of symptom onset, and compensatory enhanced conduit function becomes essential in this situation. Early exercise-induced symptoms may also be related to conduit function failure in the setting of impaired reservoir function.³³ Advanced symptomatic HFpEF is characterized by an eventual impairment in all three atrial functional phases³⁴ (Figures 2 and 3).

Hewing et al demonstrated that in patients with sinus rhythm, LA reservoir, conduit, and contractile function all inversely correlated with pulmonary capillary wedge pressure. However, LA contractile strain could independently predict invasively measured pulmonary capillary wedge pressure with a higher diagnostic accuracy than average E/E' ratio.³⁵ Furthermore, Lundberg et al found LA strain to outperform the current guideline-recommended algorithm incorporating E/e', LA volume index, and max tricuspid

regurgitation velocity in determining invasively measured elevated pulmonary capillary wedge pressure.³⁶

Impaired LA reservoir strain may provide enhanced diagnostic accuracy beyond conventional echocardiographic measures to discriminate true HFpEF from noncardiac dyspnea.³⁷ Impaired resting LA reservoir strain is associated with decreased peak oxygen consumption.³⁸ LA reservoir strain normally increases during exercise, but this typical exercise-related augmentation is blunted in symptomatic patients. Impaired LA reservoir augmentation with exercise leads to right ventricular-pulmonary circulation uncoupling and exercise ventilatory inefficiency.³⁹ Furthermore, resting LA reservoir strain may outperform LV GLS in its diagnostic utility and prognostic ability for the prediction of heart failure hospitalization.³⁸

4 | RIGHT HEART MECHANICS

Right heart dysfunction is common throughout the clinical progression from preclinical disease to overt heart failure (Figure 1). Almost half of the patients with HFpEF have right heart dysfunction as assessed by RV longitudinal strain.³⁸ HFpEF patients with prominent right heart dysfunction may represent a particularly high-risk phenotype.⁴⁰ Although far less data examining right heart deformation in HFpEF are currently available, recommendations for the standardization of right heart deformation imaging have been published²⁶ and future study will further our understanding of right heart dysfunction.

Intact structure, function, and geometry of the inter-ventricular septum are of utmost importance in preserving RV function. Shearing forces of the oblique inter-ventricular septal fibers result in systolic twisting of the base toward the apex, leading to RV longitudinal motion. Inter-ventricular septal mechanics are normally responsible for approximately 80% of RV systolic function. Circumferential compression of the transversely oriented fibers of the RV free wall results in a bellows motion, which normally contributes approximately 20% of RV systolic function.^{41,42} RV dysfunction initially involves reduced longitudinal performance with a compensatory increase in circumferential motion; therefore, RV longitudinal strain may serve as a sensitive tool for identifying early dysfunction.

Asymptomatic patients with metabolic disease commonly exhibit mild reductions in RV longitudinal strain.^{43,44} With disease progression into symptomatic heart failure, almost half of the HFpEF patients have RV dysfunction by deformation indices³⁸ (Figure 2). RV longitudinal strain and global longitudinal early-diastolic strain rate (RV-SRe) are both more significantly impaired in patients with symptoms than in those with preclinical disease.⁴⁵ Right heart dysfunction may occur as a result of resting pulmonary hypertension or exercise-induced pulmonary hypertension. However, in some patients LV GLS may be a more important predictor of impaired RV longitudinal function than pulmonary arterial systolic pressure,⁴⁵ suggesting a global myocardial process as the driver of dysfunction as opposed to pulmonary hypertension alone. Nonetheless, indices incorporating simultaneous RV function and afterload provide a measure of RV performance and pulmonary circulation coupling. Among patients with HFpEF, the ratio of RV longitudinal strain to pulmonary

artery systolic pressure independently predicted the composite endpoint of all-cause death and HF hospitalization, even after multivariate adjustment.⁴⁶

Impairment of right atrial deformation has also been appreciated in HFpEF patients.⁴⁷ Pulmonary hypertension is associated with a decrement in right atrial strain.⁴⁸ Right atrial mechanics may prove an indicator of systemic venous congestion and related cardiorenal dysfunction. A distinct HFpEF phenogroup characterized by extensive cardiac remodeling with prominent pulmonary hypertension and right heart failure exists.⁴⁰ This phenogroup more often includes elderly patients with chronic kidney disease and appears to be at particularly high risk.

5 | POTENTIAL OF MACHINE LEARNING

Heart failure with preserved ejection fraction is heterogeneous entity affected by multiple clinical variables and structural alterations. Current methods resort to an oversimplified approach for assessment and risk stratification.⁴ This one size fits all approach has not proved applicable in clinical practice. With the evolution of technology and computer capabilities, artificial intelligence (AI) is opening new frontiers in cardiovascular imaging. Machine learning (ML), a subset of AI, is ushering a new era in cardiovascular imaging by expanding boundaries not limited by conventional statistics.⁴⁹ Unlike traditional approaches, ML can decipher hidden patterns and extrapolate hidden patterns within vast data matrices.^{50,51} This technology can integrate diastolic indices and speckle tracking echocardiography to offer innovative insights into HFpEF⁵² (Figure 4).

Lancaster et al performed an unsupervised, hierarchical cluster analysis of 866 patients with diastolic dysfunction graded using contemporary ASE recommendations.⁵³ Major adverse cardiovascular events, hospitalization, and mortality were compared between conventional and duster-based categorizations. Survival analyses of patients assessed by clustering algorithms showed improved prediction of event-free survival by cluster analysis over diastolic grade classifications for all-cause mortality and cardiac mortality.

Omar et al performed a cluster analysis of LA and LV mechanical deformation parameters that resulted in a Doppler-independent phenotypic characterization of diastolic function and provided a noninvasive estimation of LV filling pressures.⁵⁴ Speckle tracking features independently clustered patients into three groups (Figure 4) with conventional parameters verifying increasing severity of dysfunction and LV filling pressure. Subsequent investigations from the same group lead to a refined ML model for assessing LV filling pressure using fourteen speckle tracking variables.⁵⁵ This model correctly identified 80% of patients with pulmonary capillary wedge pressure ≥ 18 mm Hg.

Machine learning has also been applied to resting and stress deformation imaging. Tabassian et al explored the role of ML in analyzing LV long-axis mechanics during stress and rest in 100 patients including those with HFpEF and healthy, hypertensive, and breathless control subjects.⁵⁶ A ML algorithm was used to model spatiotemporal patterns of the speckle tracking traces and compare the ML algorithm predictions with the clinical diagnoses. The ML algorithm predicted symptoms with a high degree of accuracy and assigning

subjects into four phenotypic groups. ML incorporating strain rate, compared with standard measurements, provided the greatest improvement in accuracy for predicting symptoms and 6-min walk distance. Sanchez-Martinez et al also utilized measurements of LV deformation at rest and exercise to examine differences between HFpEF and healthy patients from the MEDIA study (MEtabolic road to DIAstolic heart failure).⁵⁷ LV long-axis myocardial velocity patterns analyzed using an unsupervised ML algorithm identified a continuum from health to disease, including a transition zone associated with an uncertain diagnosis. As we move forward in the current era of cardiovascular imaging, ML algorithms will be increasingly integrated into clinical practice and cardiovascular research. These methods may help detect previously unrecognized phenotypes and tailor individualized therapies.⁴

6 | CONCLUSION

Heart failure with preserved ejection fraction is a complex clinical entity mediated by multiple clinical factors leading to various structural alterations. Risk factor exposure leads to an evolution of abnormal myocardial mechanics in each cardiac chamber. Initially, many deformation parameters only deteriorate during exercise. Although common mechanical changes are often present, significant heterogeneity in structure and function may exist. In addition to multiple imaging biomarkers, heterogeneity of clinical features and associated medical conditions adds to the complexity of this syndrome. Current methods resort to an oversimplified approach for assessment and risk stratification. With the evolution of technology and computer capabilities, artificial intelligence (AI) is opening new frontiers in cardiovascular imaging. This technology can be integrated with diastolic indices and speckle tracking echocardiography to offer innovative insights into HFpEF.⁵²

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FIGURE 1.

Temporal evolution of myocardial mechanics. *Modified from Bianco et al.⁴ LV = left ventricular, LA = left atrial, RV = right ventricular

FIGURE 2.

Parameters of myocardial mechanics in HFpEF. A, Impairment of left ventricular global longitudinal strain and mechanical dispersion are common HFpEF mechanical changes. B, Reductions in left atrial reservoir, conduit, and contractile function commonly encountered in symptomatic HFpEF. C, HFpEF-associated impairment of right ventricular free wall and four-chamber deformation. D, Despite normal or near normal tissue Doppler-derived parameters of diastolic function, significant deteriorations of mechanical deformation may exist. LAScd = left atrial strain during conduit phase; LASct = left atrial strain during contraction phase; LASr = left atrial strain during reservoir phase; LV GLS = left ventricular global longitudinal strain; RV4CSL = right ventricular four-chamber strain; RVFWSL = right ventricular free wall longitudinal strain

FIGURE 3.

Temporal evolution of left atrial failure. Preclinical dysfunction is associated with a reduction in reservoir and conduit function, while relative contractile function remains normal or increased. Atrial contractile failure, along with further reductions in reservoir and conduit function, is associated with symptom onset. Advanced symptomatic HFpEF is characterized by an eventual decrement in all 3 atrial strain phases

FIGURE 4.

Clustering dendrograms for conventional variables and their STE correspondents.

*Reprinted with permission from Omar et al.⁵⁴ Clustering dendrograms using STE and conventional variables together. The dissimilarity matrix is given as a heat map of Euclidean distance (red). The AU (red numbers) and bootstrap probability (BP) (green numbers) were calculated. AU values are shown only for leaflets that had an AU > 95% (considered statistically significant). Significant proximity of variables in the clustering leaflets was decided using 2D-LAVmax, E/e', A-wave velocity, and a' velocity were shown to be in perfect proximity with their STE counterparts STE-LAV max, VR-E/SR-E_{AV}, VR-A_{AV}, and SR-A_{AV}, respectively (AU = 97%, 96%, 98%, and 100%, respectively). The conventional parameters e'/a' and E/A were also in significant proximity to their STE counterparts SR-E/SR-A_{AV} and VR-E/VR-A_{AV}, respectively (AU = 98%), and also between e' and s' and their STE counterparts SR-E_{AV} and SR-S_{AV}, respectively (AU = 100%). 2D = 2-dimensional; AU

= approximated unbiased probability; E = pulsed-Doppler-derived mitral flow early-diastolic velocity; E/A = Doppler-derived mitral flow early to late diastolic velocity ratio; E/e' = ratio of Doppler-derived mitral flow early-diastolic velocity to tissue Doppler-derived mitral annular early-diastolic velocity; E' = tissue Doppler-derived mitral annular early-diastolic velocity; LAV = left atrial maximum volume; SR-A_{AV} = peak atrioventricular strain rate during atrial contraction; SR-E/SR-A_{AV} = ratio between atrioventricular strain rate at early diastole and during atrial contraction; SR-E_{AV} = early-diastolic peak atrioventricular strain rate; STE = speckle tracking echocardiogram; TLVd = total left heart volume during ventricular diastole; TLVs = total left heart volume during ventricular systole; VR-A_{AV} = peak atrioventricular volume expansion rate at left atrial contraction; VR-E = rate of volume expansion at early diastole; VR-E/SR-E_{AV} = ratio between atrioventricular volume expansion rate and strain rate at early diastole; VR-E_{AV} = early-diastolic peak atrioventricular volume expansion rate; VR-E-VR-A_{AV} = ratio between atrioventricular volume expansion rate at early diastole and during atrial contraction