

## Teasing Apart Heart Failure With Preserved Ejection Fraction Phenotypes With Echocardiographic Imaging Potential Approach to Research and Clinical Practice

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**Phenotyping heart failure represents a major challenge for both research studies and clinical practice. Large-scale clinical trials have failed to achieve meaningful improvement in clinical outcomes with different pharmacological agents in patients with heart failure and preserved left ventricular ejection fraction. Therefore, an alternative scheme for phenotyping heart failure is needed, which is both pathophysiologically distinct and practical for routine clinical application.**

Heart failure is a syndromic diagnosis broadly based on clinical features, physical findings, and serum biomarkers. Although the assessment of exercise hemodynamics and invasive estimation of filling pressures may be necessary, it is typically confirmed and phenotyped by the imaging data. Phenotyping heart failure represents a major challenge despite decades of ongoing research, vast clinical experience in the field, and multiple iterations of published guidelines. Left ventricular ejection fraction (LVEF) remains the major phenotyping tool endorsed by multiple cardiology societies. However, it has multiple limitations especially in patients with heart failure with preserved LVEF (HFpEF), and many have questioned the current approach to phenotyping of heart failure but no alternative, widely accepted, scheme (which is both clinically relevant and practical) has been offered.<sup>1</sup>

The existing phenotyping approach to heart failure is based on the premise of LVEF as a surrogate marker for left ventricular systolic performance and, in turn, prognosis. Heart failure patients with reduced LVEF (HFrEF) are assumed to have systolic heart failure, whereas many heart failure patients have preservation of LVEF and are commonly labeled as

HFpEF. This assumption makes LVEF the primary marker of heart failure and excludes other important abnormalities that can create the heart failure syndrome. Furthermore, LVEF is an imperfect marker even for assessment of systolic function: it has high interobserver variability, it mainly reflects radial shortening, it is load dependent, and it does not reflect the remodeling pattern of the left ventricle in isolation.<sup>2</sup> It is clear that the current scheme (isolated application of LVEF) does not capture the whole spectrum of left ventricular systolic performance abnormalities and needs to be reevaluated.<sup>2,3</sup>

### Current Approach to Phenotyping Heart Failure

The emergence of LVEF as the cornerstone of the current heart failure phenotyping is linked to the success of multiple studies in patients with HFrEF based on the pathophysiologic concept of neurohumoral activation. The disappointment came when the concept of neurohumoral activation in heart failure was applied to patients with HFpEF: large studies have failed to reproduce the outcome benefits with pharmacological agents that work well in patients with HFrEF. The reasons for these failures lie not only in significant pathophysiologic differences between the entities of HFrEF versus HFpEF but rather in marked heterogeneity of patients who have the clinical features of HFpEF<sup>1</sup>; this group might even include patients with systolic dysfunction that could not be picked up using ejection fraction cut points or those with low EF that recovered. Patients with HFrEF have transmural myocardial dysfunction resulting in reduced ejection, which serves as a unifying pathophysiologic feature.<sup>4</sup> In patients with HFpEF, LVEF itself is a poor surrogate of left ventricular systolic performance and cannot be used as a single measure to describe the patient's phenotype. To compound this uncertainty, major societies added another phenotype called midrange or borderline LVEF patient category that largely lacks validated characterization in terms of prognosis or response to therapy. Vast majority of these patients have impaired systolic function and longitudinal shortening. In one study of patients with HFpEF, all patients with LVEF between 45% and 50% had reduced longitudinal systolic function.<sup>5</sup> The decreased precision of echocardiographic estimation of LVEF in the midrange should also be acknowledged because it often leads to misclassification of these patients.

HFpEF is currently phenotyped by what it is not (ie, it is not HFrEF) rather than what it is (a basket of varying pathophysiologic abnormalities). Diastolic dysfunction caused by left ventricular stiffening and impaired relaxation has been considered

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the cornerstone of HFpEF.<sup>1</sup> In reality, one should keep in mind considerable limitations of the conventional echocardiographic tools for assessing diastolic function. HFpEF is a complex and heterogeneous entity with varying contributions of several underlying pathophysiologic substrates including myocardial dysfunction and subsequent fibrosis, vascular stiffening, and impaired ventriculoarterial coupling, and extracardiac components such as obesity, renal dysfunction, etc (Online Figure I).<sup>1</sup> Identifying and quantifying the degree of myocardial dysfunction in this complex cascade is a challenge but the one that will determine the success of future studies.

### Longitudinal Systolic Dysfunction

If we continue to think that heart failure is best classified based on left ventricular dysfunction, it is reasonable to suppose that a method that better identifies left ventricular dysfunction would improve our ability to phenotype. To be clinically meaningful in phenotyping heart failure patients, any measurement tool should ideally meet the following criteria: pathophysiologic justification, validation as a prognostic marker, and practical applicability for widespread clinical use. On the basis of these criteria, longitudinal systolic dysfunction as measured by 2-dimensional global longitudinal strain (GLS) can serve as a phenotyping tool in patients with HFpEF (Online Table I).<sup>6</sup> GLS is relatively independent of certain well-known measures of longitudinal relaxation such as  $e'$  velocity and  $E/e'$  ratio.<sup>5</sup> It preferentially reflects the performance of subendocardial fibers, which are commonly affected early during the myocardial disease.<sup>4</sup> In asymptomatic individuals, attenuation of GLS has been associated with many conditions that are likely to affect the myocardium such as hypertension, diabetes mellitus, and subclinical atherosclerosis.<sup>7</sup> In patients with HFpEF, a varying degree of impaired longitudinal systolic function has been demonstrated. Although longitudinal strain generally correlates with LVEF, in patients with HFpEF, this correlation is relatively modest.<sup>8</sup> Importantly, GLS values likely reflect the myocardial dysfunction burden and myocardial fibrosis. In a study by Kraigher-Krainer et al,<sup>5</sup> impaired GLS was associated with higher natriuretic peptide levels after adjustment for baseline covariates including LVEF, measures of diastolic function, and left ventricular filling pressures. In another study of patients with HFpEF, impaired GLS was linearly associated with natriuretic peptide levels and a circulating collagen synthesis biomarker.<sup>9</sup> In a substudy of the TOPCAT trial (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist), GLS was the strongest echocardiographic predictor of the composite outcome including cardiovascular death, heart failure hospitalization, or aborted cardiac arrest.<sup>6</sup> The association of GLS with adverse cardiovascular outcomes was similar between the subgroups of patients with LVEF  $\geq 55\%$  and patients with midrange LVEF, suggesting that longitudinal strain adds a prognostic value beyond LVEF.<sup>8</sup>

In terms of practicality, GLS derived by 2-dimensional speckle tracking echocardiography is fairly reproducible and is more reliable than other 2-dimensional speckle tracking-derived measures of myocardial mechanics such as circumferential strain and left ventricular twist.<sup>10</sup> Importantly, semiautomated software tools can be applied to derive GLS with high accuracy and efficiency.

Application of GLS to research and clinical practice is clearly not free of challenges. Intervendor variability remains a major issue. The lack of universally accepted cutoff values that define abnormal GLS is also an issue, but based on the available evidence, the cutoff of  $-16\%$  for defining abnormal GLS in patients with HFpEF may be reasonable and practical (Online Table II). Poor acoustic windows can limit adequate image acquisition for strain analysis in some patients.<sup>10</sup>

### Emerging Phenotypic Categories of HFpEF

It is likely that GLS will allow better classification of the heart failure syndrome and may identify prognostic and possibly therapeutic subsets not possible with ejection fraction alone. Emerging data seem to offer some preliminary support for such a strategy, especially in HFpEF.

Heart failure with preserved ejection and preserved longitudinal systolic function (HFpEF-pLS) might possibly indicate early stage or lesser degree of myocardial dysfunction and should prompt investigation of contributing mechanisms for heart failure syndrome (Online Figure I) and direct therapies based on the dominant pathophysiologic construct.

Volume overload is an obvious target for therapy in patients with heart failure. Cardiorenal interactions in heart failure patients are complex and are mediated by hemodynamic abnormalities (such as renal congestion), vascular dysfunction, intrinsic renal disease, and inflammatory/humoral factors.<sup>1</sup> Vascular compliance abnormalities are essential in pathogenesis of HFpEF because impaired arterial properties likely mediate diminished exercise tolerance and later left ventricular dysfunction. Impaired ventriculoarterial interaction with exercise and reduced endothelium-dependent vasodilation are well described in patients with heart failure and preserved LVEF.<sup>11</sup> Both these might respond well to targeted therapies aimed at increasing NO availability like inorganic nitrates.

Left atrial dysfunction has been shown to correlate with the degree of diastolic dysfunction and seems to contribute to heart failure hemodynamics and adverse prognosis.<sup>12</sup> Atrial fibrillation, a consequence of left atrial dilation and dysfunction, is strongly associated with HFpEF and could be a target for therapy in such patients. Coronary artery disease and myocardial ischemia have been implicated in pathogenesis of HFpEF and seem to have prognostic relevance.<sup>13</sup> It has been suggested that revascularization can preserve cardiac function and improve outcomes in these patients, but further prospective studies are needed.<sup>13</sup>

Obesity is strongly implicated in pathogenesis of HFpEF, has multiple potential mechanisms for mediating heart failure, and presents an attractive target for intervention.<sup>14</sup> The increase in heart volumes in obese patients is associated with greater pericardial restraint and heightened ventricular interdependence, which could be a potential target in future.<sup>14</sup> Also, adiposity-related inflammation is an important pathophysiologic factor affecting both the myocardium and the vasculature.

Heart failure with preserved ejection and reduced longitudinal systolic function (HFpEF-rLS) identifies patients with measurable degree of myocardial dysfunction despite

LVEF of  $\geq 50\%$  (Online Figure I). Several important pathways lead to myocardial damage because of long-standing effects of cardiovascular risk factors. Abnormal calcium currents and reduced sensitivity of intracellular proteins to calcium result in impaired excitation–contraction coupling and contribute to myocardial systolic dysfunction. The underlying pathology includes cardiomyocyte hypertrophy, deposition of glycation end products, and interstitial fibrosis with increased myocardial stiffness. Systemic inflammatory response also contributes to myocardial dysfunction and multiorgan involvement in these patients.<sup>1</sup> Many of these changes detectable by GLS are present at a time when they do not reduce ejection fraction. Identifying patients with established HFpEF-rLS also has clinical implications. These patients are more likely to have higher left ventricular volumes and left ventricular mass index.<sup>5,6</sup> Targeted therapies (such as an aldosterone antagonist) might be more effective in this group of patients.<sup>6</sup> In elderly patients with HFpEF-rLS, the longitudinal deformation pattern can help identify cardiac amyloidosis, an underdiagnosed entity. Significant decrease in GLS, apical sparing of longitudinal strain, and high LVEF/GLS ratio should prompt further testing for cardiac amyloidosis.

In all cases, an integrative and comprehensive approach is essential with careful consideration of mimickers and contributing factors. Constrictive pericarditis is a consideration with HFpEF-pLS phenotype: longitudinal systolic function is commonly preserved in patients with constrictive pericarditis, whereas circumferential function and twist mechanics may be impaired.

### Unanswered Questions and Future Directions

Although the phenotyping approach to HFpEF using longitudinal systolic function is attractive, it largely lacks clinical validation at this time. Post hoc analysis of HFpEF trials may show distinct segregation of HFpEF-rLS and HFpEF-pLS phenotypes in regard to response to medical therapy.<sup>6</sup> In addition, comprehensive phenotyping tools using cluster analysis, gene expression, and proteomics may also demonstrate differences between these phenotypes. Large studies using similar schemes are warranted and should focus on a variety of outcome measures such as functional and exercise characteristics (peak  $\text{VO}_2$ , 6-minute walking test, etc), echocardiographic measures, cardiac biomarker changes, and clinical follow-up events (hospitalization rates, mortality, etc). Patients with HFpEF-rLS could be a target for studies involving disease-modifying agents like angiotensin and aldosterone antagonists while studies in the HFpEF-pLS phenotype could initially focus on identifying, quantifying, and targeting the predominant pathophysiologic features, such as vascular noncompliance, obesity, and volume overload.

### Conclusions

It has become obvious in recent years that HFpEF is a complex entity with different pathophysiologic components beyond the myocardial dysfunction itself. The ability to identify myocardial dysfunction as the predominant pathophysiologic mechanism is an essential step in a phenotyping HFpEF

because other mechanisms and contributing factors might also lead to heart failure syndrome. Using the proposed framework may help in designing future clinical trials and will likely result in uncovering successful therapies.

### Disclosures

None.

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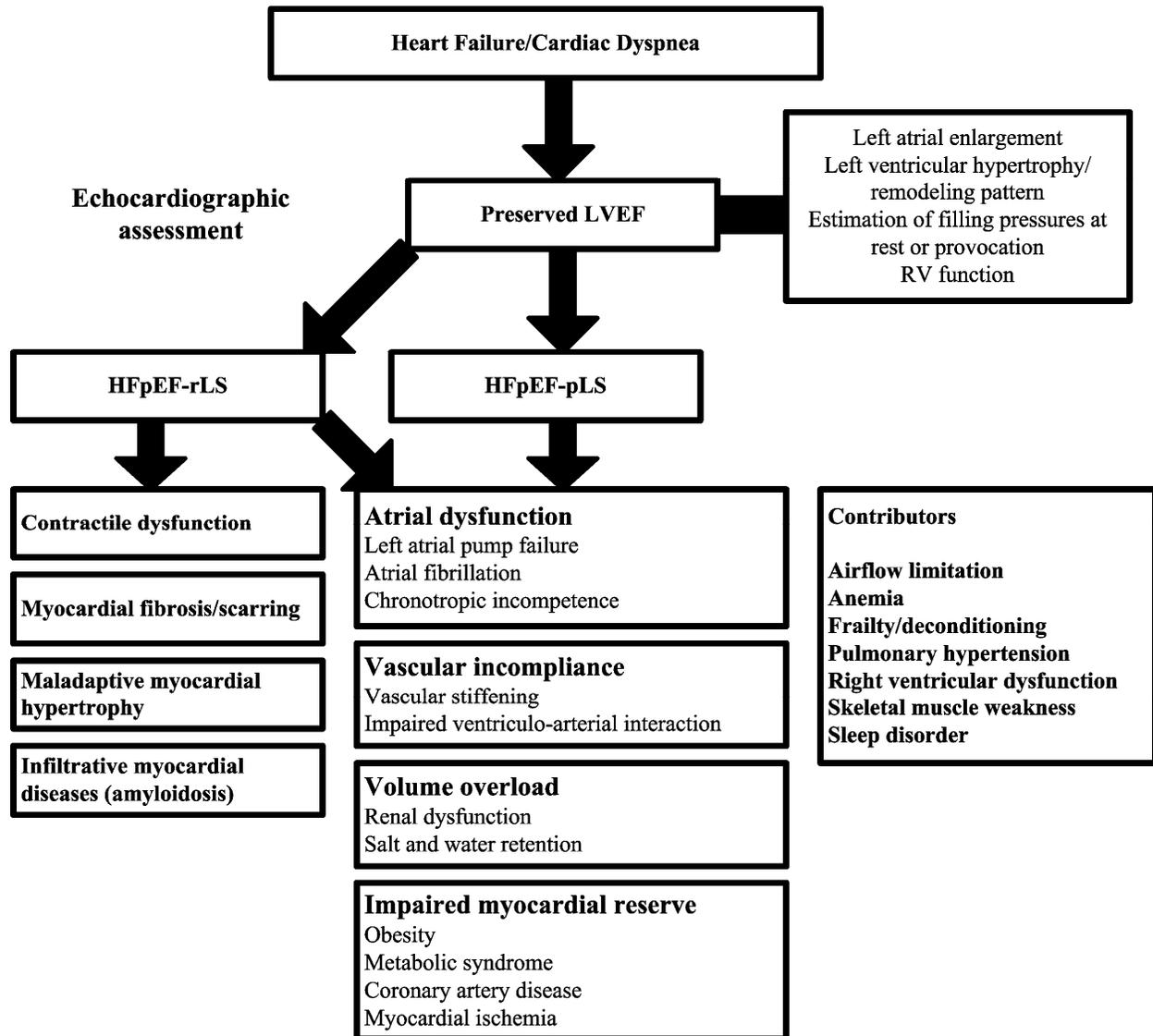
# VIEWPOINTS

## Teasing Apart Heart Failure with Preserved Ejection Fraction Phenotypes with Echocardiographic Imaging

Potential Approach to Research and Clinical Practice

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### Online Supplement



**Online Figure:** Complex pathophysiology of heart failure with preserved ejection fraction (HFpEF). HFpEF is a complex and heterogeneous entity with varying contributions of different pathophysiologic components. HFpEF-pLS indicates heart failure with preserved LVEF and preserved longitudinal systolic function; HFpEF-rLS, heart failure with preserved LVEF and reduced longitudinal systolic function; LVEF, left ventricular ejection fraction; and RV right ventricle.

**Online Table I.** Phenotyping heart failure using left ventricular ejection fraction and longitudinal systolic function

Proposed phenotype	Current designation	Left ventricular ejection	Longitudinal function	Natriuretic peptides
Heart failure with reduced ejection fraction and reduced longitudinal systolic function (HFrEF-rLS)	Heart failure with reduced ejection fraction, heart failure with mid-range ejection fraction	Reduced or 'mid-range'	Reduced	+++
Heart failure with preserved ejection fraction and reduced longitudinal systolic function (HFpEF-rLS)	Heart failure with preserved ejection fraction	Preserved	Reduced	- to ++
Heart failure with preserved ejection fraction and preserved longitudinal systolic function (HFpEF-pLS)	Heart failure with preserved ejection fraction	Preserved	Preserved	- to +

**Online Table 2.** Selected studies reporting global longitudinal strain thresholds in patients with heart failure with preserved ejection fraction

Study	N	Cutoff for abnormal GLS	Prevalence of abnormal GLS	Vendor used	Reported outcomes
PARAMOUNT, 2014 <sup>1</sup>	219	-15.8%	67%	TomTec (Munich, Germany)	Associated with natriuretic peptide levels
TOPCAT, 2015 <sup>2</sup>	447	-15.8%	52%	TomTec (Munich, Germany)	Predictive of cardiovascular death and hospitalization
RELAX, 2017 <sup>3</sup>	187	-16.0%	65%	TomTec (Munich, Germany)	Associated with natriuretic peptide levels and a circulating collagen synthesis biomarker
Donal et al, 2017 <sup>4</sup>	237	-16.0%	67%	EchoPAC (Norten, Norway)	Associated with worse composite outcome of mortality and re-hospitalization
Buggey et al, 2017 <sup>5</sup>	739	-16.0%	76%	TomTec (Munich, Germany)	Associated with worse composite outcome of mortality and re-hospitalization

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