Imaging fibrosis in heart failure with preserved ejection fraction

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Abstract

Increased myocardial fibrosis is considered to be a key underlying pathological mechanism in heart failure with preserved ejection fraction (HFpEF), with increased myocardial stiffness resulting in left ventricular dysfunction. Direct measurement of fibrosis via histology is not feasible; however, noninvasive imaging approaches now offer the potential for quantification. Improved fibrosis assessment in HFpEF should facilitate earlier disease detection, targeted treatment, and improved prognostication. This review highlights the importance of fibrosis in HFpEF and introduces the various contemporary multimodality imaging technologies available for quantification. We focus on T1 mapping and extracellular volume quantification by cardiac magnetic resonance imaging and outline the current evidence and potential future applications. ■ *Heart Metab*. 2016;71:18-22

Keywords: HFpEF; myocardial fibrosis; T1 mapping

Introduction

The management of heart failure with reduced systolic function (also known as heart failure with reduced ejection fraction [HFrEF]) has progressed over the last few decades with the ability to dramatically enhance life span by treatment with angiotensin-converting enzyme (ACE) inhibitors, β-blockade, and mineralocorticoid receptor antagonists. However, in heart failure where ejection fraction is preserved (called HFpEF), mortality rates have remained static, and management has relied on symptomatic treatment, with no prognostic therapies available despite numerous trials.[1] This is largely because HFpEF represents an amalgam of different underlying etiologies, and we are currently unable to accurately stratify the disease according to underlying mechanism. In turn, this limits the scope for innovation of targeted therapies that reduce the considerable morbidity and mortality associated with this condition.

Increased interstitial myocardial fibrosis is thought to be a major determinant of the reduced myocardial compliance that characterizes HFpEF. Until recently, cardiac imaging methods have not been able to quantify fibrosis and have been limited to downstream measures of remodeling and ventricular dysfunction.[2] Quantification of myocardial fibrosis may provide important prognostic information in HFpEF and permit disease stratification to guide therapy.

Abbreviations

ECM: extracellular matrix; **ECV:** extracellular volume; **GBCA:** gadolinium-based contrast agent; **HFpEF:** heart failure with preserved ejection fraction

Patterns of fibrosis in disease and imaging correlates

Myocardial fibrosis can be reparative or reactive. Both lead to increasing stiffness and ultimately to ventricular dysfunction. There are different patterns of fibrosis, dependent on the underlying disease pathology, but in all there is extracellular matrix (ECM) remodeling with excess collagen (predominantly types I and III). Focal replacement fibrosis is present in myocardial infarction and many other non-ischemic pathologies and correlates with clinical outcome. In contrast, with HFpEF, changes occur in the ECM due to a number of different metabolic and hemodynamic factors, including hypertension, diabetes, and renal failure,[3] leading to reactive diffuse interstitial fibrosis.[4]

Endomyocardial biopsy is the gold standard for assessing fibrosis; however, it is prone to sampling error and because it is invasive, is rarely performed. Although interstitial fibrosis is reversible[5] and a key target for several current and pending therapies,[6] its diffuse nature makes it hard to identify noninvasively. Therefore, until recently, diagnosis of fibrosis in HFpEF relied on assessing the functional consequences.

Functional imaging for evidence of fibrosis in HFpEF

Increased mass and chamber geometry is a common structural abnormality of the heart in HFpEF, and sensitivity has improved from M-mode, two-dimensional, and now three-dimensional technology (which appreciates regional changes). Mitral valve blood flow assessed by Doppler echocardiography, combined with pulmonary vein assessment and left atrial size, is abnormal in virtually all patients with HFpEF and relatively easily measured. Tissue velocities (tissue Doppler) help in borderline patients, and new parameters such as strain imaging or speckle tracking have potential use as a more reproducible measure, independent of tethering and translational cardiac motion.[7]

Studies suggest that diastolic dysfunction due to hypertension and left ventricular hypertrophy may be reversible with treatment,[8] yet these findings have not been replicated more generally in clinical HFpEF. Furthermore, echocardiographic measures of diastolic function are often observed in patients without heart failure and are variable within each individual, being influenced dynamically by other physiological factors, such as loading conditions. In part, this is because functional measurements only capture the downstream effects of fibrosis.

Techniques have been developed to directly image the pathways of collagen metabolism and regulation, such as radiolabeled losartan, matrix metalloproteinases in animal models, and collagen-specific contrast agents.[9–11] Such technology shows promise in animal models and after myocardial infarction but has not been translated into clinical practice. Therefore, the current functional biomarkers need to be supported by imaging methods for tissue characterization in order to detect and quantify fibrosis.

Noninvasive methods for quantitative assessment of myocardial fibrosis

Echocardiography: integrated backscatter

Ultrasonographic tissue characterization uses frequency-dependent attenuation and dispersion as a correlate of fibrosis, known as "integrated backscatter" (IBS). Validation work has been performed both against histology and serological markers of fibrosis,[12] and the technique has been shown to differentiate controls from patients with muscular dystrophy and scleroderma, and it correlates with myocardial biopsy in dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM).[13] Yet larger studies are elusive, and the technique appears unreliable despite early promise,[14] with limitations by acoustic windows and influences from other factors such as angiogenesis.

Nuclear medicine: perfusable tissue index

The perfusable tissue index (PTI) offers a way to assess fibrosis by evaluating the ratio of perfusable to total tissue using radioisotope tracers imaged with positron emission tomography.[15] It correlates with

cardiovascular magnetic resonance (CMR) tissue tagging suggesting an association with fibrosis, though more recent work has concentrated on viability assessment.[16]

Cardiovascular magnetic resonance imaging: T1 mapping and extracellular volume quantification

Gadolinium-based contrast agents (GBCA) are extracellular contrast agents that passively persist in infarcted tissue and have been used extensively to image scar tissue. Such tissue can be imaged using the late gadolinium enhancement (LGE) technique, with normal myocardium artificially "nulled" to appear black by operator manipulation of the magnetic resonance sequence. The utility of LGE imaging is limited in HFpEF both because of the global nature of the pathology and the fact that the degree of fibrosis is generally below the limits of detection for the technique. T1 mapping may help. T1 (longitudinal relaxation time, expressed in milliseconds) and also T2 ("true" transverse relaxation time) and T2* ("observed" T2) are magnetic properties of tissue. These change with pathology, and of these, mapping of T1 is the most promising. These relaxation times can be calculated on a voxel by voxel basis and represented on a clinically intuitive color map. There are a number of different sequences that vary inversion pulses and readout timings, originating from modified Look-Locker inversion recovery (MOLLI).[17] Each sequence has variable precision, repeatability, and theoretical accuracy, as well as varying tradeoffs in breath-hold duration and resolution. Attempts to standardize T1 mapping techniques are ongoing and important for widespread uptake.[18,19]

As GBCA does not pass through intact cell membranes, it provides a way to dichotomize the intra- and extracellular myocardium using T1 mapping. This therefore provides promise for application in HFpEF where fibrosis accumulates in the ECM, meaning that there will be GBCA accumulation and shortening of T1. Comparing T1 values before and after introduction of GBCA negates some of the issues of reproducibility and standardization, as it is the change in T1 values, rather than absolute value, that is measured. The extracellular volume (ECV) fraction can then be calculated by correcting for the volume of distribution through hematocrit sampling, thus reflecting changes in the ECM. It can now be performed without blood

testing (blood T1 approximates hematocrit) and calculated on the scanner itself, significantly simplifying the technique.

ECV and post-contrast T1 both have potential application in HFpEF. ECV expansion correlates with both invasive and noninvasive measures of diastolic function and filling pressures[20–24] and directly tracks changes that result in a noncompliant heart.[25] Moreover, it predicts outcome in HFpEF and correlates with ECM on histology.[26] Kammerlander et al[27] found that in 473 patients (246 with HFpEF), ECV predicted prognosis the most strongly of all imaging biomarkers and remained in multivariate models when combined with clinical variables (unlike ejection fraction or B-type natriuretic peptide [BNP]). Before widespread application in HFpEF, these techniques need to be demonstrated to robustly track disease in clinical trials; many are currently in progress (see *Table I*).

Fibrosis quality or quantity?

In early disease, T1 mapping could be useful for risk stratification and to direct therapy. However, the road is not without difficulty. Differences between normal and abnormal tissue can be small,[28] and therefore fibrosis detection may be limited by precision and overlap between healthy and patient populations. Moreover, the quality rather than the quantity of ECM change per se may be important. Collagen cross-linking has recently been shown to have an important role in determining left ventricular stiffness,[29] as do other structural proteins such as titin.[30]

In the context of HFpEF though, T1 mapping has an additional role in identifying rare causes of HFpEF due to infiltrative disease. Gross expansion of the extracellular space in amyloidosis is readily detected (high pre-contrast T1), as is intracellular accumulation of iron (hemochromatosis) or glycosphingolipid (Anderson-Fabry disease) deposition, both causing low T1. As ECV also permits analysis of myocyte volume, a low ECV may also distinguish adaptive from maladaptive pathology in athletes who have myocyte hypertrophy.[31]

Cardiac amyloidosis

Senile wild-type transthyretin amyloidosis (wtATTR) is underrecognized in HFpEF. One HFpEF autopsy study showed moderate or severe infiltration in 5%

of patients and mild infiltration in 12%.[32] wtATTR demands recognition as a different disease with poor prognosis but potential new treatment options.[33] It shares a common pathway in diastolic dysfunction with HFpEF; however, relatively speaking, there is massive ECM expansion due to amyloid fibril deposition (rather than fibrosis). This is easily picked up both by pre-contrast T1 mapping and ECV; the latter is elevated up to 45% in amyloid versus 25% in control populations (only a few percent higher in diffuse fibrosis). Importantly, occult amyloid may be a disease in a broader elderly population than HFpEF, and when present, it appears to drive outcomes in aortic stenosis more than valve stenosis itself.[34]

Conclusion

Preventing or reversing interstitial fibrosis is a therapeutic target in HFpEF; however, accurate and reproducible noninvasive methods for detection and quantification are needed. Imaging offers a potential solution, with both functional and quantitative techniques available; T1 mapping and ECV quantification using cardiac magnetic resonance imaging are currently the most promising. Incorporating these markers into clinical trials may be a necessary step in development of better therapies and ultimately in providing pathophysiology-based disease stratification in this population. ■

Trial	Abbreviated trial names	Identifier	Number	Primary end point	Secondary end point
Renal Denervation in Heart Failure Patients With Preserved Ejection Fraction	RESPECT-HF	NCT02041130	144	Changes in left atrial volume index; left ventricular mass index on CMR imaging	The biomarkers of cardiac interstitial fibrosis as assessed by plasma assays, imaging markers of cardiac fibrosis
Left Ventricular Stiffness vs Fibrosis Quantification by T1 Mapping in Heart Failure with Preserved Ejection Fraction	STIFFMAP	NCT02459626	36	Correlation of extracellular volume [MRI] and myocardial stiffness [p-v-loops]	n/a
Understanding and Treating Heart Failure With Preserved Ejection Fraction: Novel Mechanisms. Diagnostics and Potential Therapeutics	Alberta HEART	NCT02052804	700	Percent of patients meeting new diagnostic criteria for HFpEF	CMR markers: ECV, T2 mapping phase contrast, tagging Biomarker analysis of the extracellular matrix
Women's Ischemia Study Evaluation	WISE	NCT02582021	220	Cardiovascular events	Blood proteomic biomarkers of extracellular matrix remodeling and fibrosis; Exercise CMR; LGE
New Echocardiographic Parameters for Assessment of Longitudinal Left Ventricular Function	LAX study	NCT01275963	160	Left ventricular longitudinal systolic strain (LV-LSS] in all patients	n/a
Noninvasive Evaluation of Myocardial Stiffness by Elastography	Elasto-Cardio	NCT02537041	100	Myocardial stiffness (by kPa) via novel device	n/a
Myocardial Perfusion, Oxidative Metabolism, and Fibrosis in HFpEF	HFpEF-PRoF	NCT02589977	60	Myocardial blood flow by CMR and PET; ECV	n/a
Assessment of Efficacy of Mirabegron, a New beta3-adrenergic Receptor in the Prevention of Heart Failure	Beta3_LVH	NCT02599480	297	Echo change in left ventricular mass and diastolic function	Cardiac fibrosis by CMR; Galectin,GDF15
Myocardial Performance at Rest and During Exercise in Heart Failure With Preserved Ejection Fraction	X-HF-SPECKLE	NCT01747785	21	Rest and stress strain, strain rate and torsion (two-dimensional echo]	n/a

Table I *Currently recruiting HFpEF trials that use interstitial fibrosis biomarkers as end points.*
Abbreviations: *CMR, cardiac magnetic resonance; ECV, extracellular volume; GDF15, growth differentiation factor 15; HFpEF, heart failure with preserved ejection fraction; kPa, kilopascal; LGE, late gadolinium enhancement; MRI, magnetic resonance imaging; n/a, not applicable; PET, positron emission tomography.*

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