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Novel plasma and imaging biomarkers in heart failure with preserved ejection fraction

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ABSTRACT

Existing diagnostic guidelines for heart failure with preserved ejection fraction (*HFPEF*) primarily comprise natriuretic peptides and echocardiographic assessment, highlighting the role of diastolic dysfunction. However, recent discoveries of novel plasma markers implicated in pathophysiology of heart failure and technological advances in imaging provide additional biomarkers which are potentially applicable to *HFPEF*. The evidence base for plasma extra-cellular matrix (ECM) peptides, galectin-3, ST2, GDF-15 and pentraxin-3 is reviewed. Furthermore, the capabilities of novel imaging techniques to assess existing parameters (e.g. left ventricular ejection fraction, systolic & diastolic function, chamber size) and additional derangements of the ECM, myocardial mechanics and ischaemia evaluation are addressed.

1. Introduction

Heart failure with preserved ejection fraction (*HFPEF*) is the subtype of heart failure (HF) most likely to be encountered in clinical practice in the near future and already accounts for approximately half of all HF cases [1]. Yet importantly, we appear no closer to offering effective treatments [2]. The latest *HFPEF* diagnostic guidelines [3] were published nearly eight years ago and still remain subject to debate. In the intervening period, technological advances in the fields of plasma biomarkers and imaging have further improved our understanding of this heterogeneous entity, provided insights into potential targets for therapy and improved diagnostic labeling. We review the respective merits of these newer biomarkers and consider their applicability for future use in *HFPEF* frameworks.

2. Current limitations, potential challenges and the need for biomarker development in *HFPEF*

A biomarker has been defined as a "characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention" [4]. The medical condition of interest should: be sufficiently common, significantly impact upon morbidity & mortality, be well defined and with effective treatments available. Likewise, for the biomarker being developed, it should ideally: be a stable product, discriminate between pathology and normal (and between pathologies), enhance clinical care, be acceptable to patients, exhibit a linear relation with change in pathology as well as being reproducible and replicated across multiple studies [5].

Adopting this approach to *HFPEF* reveals a series of disease- and biomarker-specific factors (see Table 1) that make biomarker development challenging [2,3,6–9]. The primary limiting factor is the marked heterogeneity that characterizes *HFPEF* populations. To date, various diagnostic criteria (including differing ejection fraction [EF] thresholds) have been employed to define *HFPEF*. Phenotypic diversity (e.g. obesity, diabetes, atrial fibrillation, right heart failure) coupled with a high prevalence of co-morbidities makes patient identification difficult. Imaging phenocopies such as hypertrophic cardiomyopathy and amyloid are additional confounders. Alternate explanations for pathophysiological mechanisms add to the uncertainty. Furthermore, the discriminatory capabilities of biomarkers (to distinguish *HFPEF* from heart failure with reduced ejection fraction [*HFREF*]) are hindered by supportive evidence to suggest the existence of both entities in continuum as part of a single syndrome. While invasive pressure assessments best illustrate the haemodynamic consequences of diastolic dysfunction (DD), they are limited by inherent procedural risks. On the other hand, non-invasive measures of DD are within normal range in up to a third of subjects. These factors highlighted above therefore ensure that existing and newer markers described in this article do not wholly fulfill the aforementioned biomarker criteria [10–16].

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Table 1
Challenges and limitations of existing biomarkers in *HFPEF*.

Disease specific factors
Population not well defined [2]
Variable diagnostic criteria in guidelines and clinical trials [2]
Confounders of diagnosis [7,8]
Phenotypic variability
High prevalence of co-morbidities may alternatively explain clinical features
Imaging phenocopies (e.g. hypertrophic cardiomyopathy, amyloid, pericardial constriction)
Atrial fibrillation (challenging clinical and imaging assessment)
No clear and effective therapies available [2]
Evidence for HFPEF as a continuum with HFREF [3,6,7]
Similar clinical signs and symptoms
Unimodal distribution of EF in clinical trials
Co-existence of systolic abnormalities and progression over time
Eccentric remodeling over time seen in hypertensives
Heterogeneity of pathophysiology [6,7,9]
Diastolic dysfunction — in *HFPEF* & *HFREF*, in normal subjects, absent in ≈1/3 of *HFPEF*
Alternate abnormalities of: ventricular–arterial coupling, arterial stiffness, systemic & pulmonary vasculature, chronotropic incompetence, endothelial function, LA function volume overloading, LV systolic function
Biomarker specific factors
Invasive approach (***assessment of diastolic dysfunction or biopsy quantification of fibrosis***)
Procedural risk
Sampling error
Non-uniform responses in end-diastolic pressure volume relationship curves
Traditional echocardiographic measures for diagnosis [10–15,43]
Not the recognized gold standard for EF, LV & LA volumes, LV mass
Limitations of methodology and feasibility, less reproducible compared to CMR
Markers of diastolic dysfunction: loading dependent
Haemodynamic disturbances may not be apparent at rest
Plasma natriuretic peptides [16]
Lower values in *HFPEF* versus *HFREF*
Lower values in obesity
Higher levels in non-*HFPEF* conditions but commonly encountered in *HFPEF*

Abbreviations: *HFPEF* = heart failure with preserved ejection fraction; *HFREF* = heart failure with reduced ejection fraction; EF = ejection fraction; LA = left atrium; LV = left ventricle.

3. Key pathophysiological substrates that comprise potential biomarkers

Various pathophysiological derangements have been implicated in *HFPEF* (see Table 1). The central disturbance remains diastolic dysfunction, which in turn is governed by myocardial stiffness [6,7]. Hypertensive heart disease accounts for a significant cohort of *HFPEF* and is associated with left ventricular hypertrophy (LVH), pressure overload, concentric remodeling and myocardial fibrosis. Structural remodeling results in alterations in both the intra- (e.g. larger cardiomyocytes and predominance of the stiffer isoform of the protein Titin) & extracellular compartments [6]. Stiffness is increased by fibrosis resulting in reduced left ventricular (LV) compliance and elevated LV filling pressures which are the haemodynamic hallmarks of *HFPEF*. Myocardial stiffness is primarily determined by the turnover rates of the extra-cellular matrix (ECM) and its constituents (predominantly collagen). However, additional factors such as inflammatory processes, endothelial dysfunction, ischaemia, and neurohormonal activation may contribute [6,7,9,16,17]. These pathological changes and consequences may be detectable by either plasma or imaging techniques (see Table 2 and Supplementary online Table 1) and form the basis of subsequent sections.

4. Novel plasma biomarkers

4.1. ECM biomarkers

Matrix metalloproteinases (MMPs) primarily degrade collagen and other ECM components while inhibitors of matrix metalloproteinases (TIMPs) counteract their actions. Generally, in *HFPEF*, TIMPs are increased and MMPs are decreased such that collagen degradation is reduced and collagen accumulation is increased. Conversely, in *HFREF* the opposite has been demonstrated [6,7,18]. However, the concept of a high TIMP/MMP ratio being synonymous with *HFPEF* is too rigid since individual MMPs and TIMPs also actively promote fibrosis through alternate (and additional) mechanisms of action [16]. The high levels of MMPs −1 [19], −2 [20–22], −8 [22], and −9 [20,21] reported in *HFPEF* likely reflect this phenomenon. In hypertensive subjects with *HFPEF*, TIMP-1 moderately predicts the presence of HF with an area under curve (AUC) of 0.71 and higher levels are detected compared to controls [18]. Additionally, TIMP-1 levels correlate with DD and are reportedly more accurate than NT-proBNP for detecting echocardiographic estimates of elevated LV filling pressures using E/E′ [19].

Compared to controls, circulating markers of active collagen turnover i.e. synthesis (e.g. pro-collagen type I carboxy-terminal pro-peptide [PICP] [19,22], collagen III N-terminal pro-peptide [PIIINP] [22]) and degradation (e.g. collagen I telopeptide [CITP]) are elevated in *HFPEF* [20,22,23]. Furthermore, elevated levels appear to correlate with worsening indices of DD [19,20,22]. In a study of 446 subjects including healthy controls (n = 241), LVH without HF (n = 144) and LVH with *HFPEF* (n = 61), a multi-biomarker panel comprising MMP-7 & -9, TIMP-1and PIIINP detected the presence of LVH (AUC = 0.8). A further panel consisting of MMP-2 & -8, TIMP-4 and PIIINP best detected LVH with *HFPEF* (AUC = 0.79) [22].

4.2. Galectin-3

Galectin-3 is a soluble β-galactoside binding protein secreted by activated macrophages, promoting fibroblast & myo-fibroblast activity and pro-collagen deposition in the ECM. Seminal studies in rat models first highlighted the potential role of Galectin-3 as a pro-fibrotic and pro-inflammatory mediator in HF [24]. While intra-pericardial infusion of galectin-3 induced adverse cardiac remodeling and LV dysfunction, these deleterious effects were counteracted by administration of its inhibitor [25]. Enhanced galectin-3 expression induces fibroblast proliferation,

Table 2
Summary of strengths and potential applicability of imaging biomarkers in *HFPEF*.

	LVEF	Contractile function (LV/LA)	Chamber quantification	ECM quantification (fibrosis)	Myocardial mechanics	Haemodynamics	CAD/ischaemia/flow reserve	Molecular imaging	Metabolic imaging
TTE	++	++	++	+	++	+++	+	n/a	n/a
CMR	+++	+++	+++	+++	+++	++	+++	+	++
PET	+	+	+	++	n/a	n/a	+++	++	++
SPECT	+	+	+	+	n/a	n/a	++	++	++
CT	+	+	+++	+	+	n/a	+	+	n/a

Adapted from Paterson et al. [100] and Jellis et al. [50].
Abbreviations: *HFPEF* = heart failure with preserved ejection fraction; LVEF = left ventricular ejection fraction; LV = left ventricle; LA = left atrium; ECM = extra-cellular matrix; CAD = coronary artery disease; TTE = trans-thoracic echocardiography; CMR = cardiac magnetic resonance; PET = positron emission tomography; SPECT = single-photon emission computed tomography; CT = computed tomography; n/a = not applicable or not assessed; + = limited evidence but potential future role; ++ = supportive evidence from either at least one large study or registry data; +++ = accepted reference standard or strongly supportive evidence base including meta-analyses or randomized controlled trials.