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Editorial

# The Harbinger of Mortality in Heart Failure With Preserved Ejection Fraction: Do GDF-15 Levels Reflect Tandem, Deterministic Effects of Fibrosis and Inflammation?

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***See article by Izumiya et al., pages 338-344 of this issue.***

Heart failure (HF) continues to have a significant clinical burden with a high rate of mortality and morbidity.[1] The European Society of Cardiology and the American Heart Association guidelines on HF classify ambulatory patients with chronic HF based on left ventricular ejection fraction (LVEF) into HF with preserved (LVEF $\geq$ 50%) or reduced (LVEF $<$ 50%) LVEF, HFPEF or HFREF, respectively.[1,2] Presently, HFPEF accounts for approximately 40% of HF diagnoses, with an increasing incidence, and mortality and morbidity comparable with HFREF.[3-5] These distinct groups of patients represent a phenotypic variation along the continuum of the HF syndrome.[6] Unlike the situation in patients with HFREF, clinical trials with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-adrenergic receptor antagonists (β-blockers), mineralocorticoid receptor antagonists, and phosphodiesterase-5 inhibitors have failed to show any consistent and significant improvement in the clinical outcomes of patients with HFPEF.

Beyond comorbidities or aggravating events, such as myocardial infarction, the development of HF can be a difficult process to detect when manifestations are subclinical. Plasma biomarkers have provided insight into the incidence and subsequent progression of HF, whereby multiple lines of evidence link 2 related processes—inflammation and fibrosis/extracellular matrix (ECM) remodelling—to HFPEF (Table 1). Plasma biomarkers have also become standard diagnostic tools, and new biomarkers are emerging to reliably discriminate HFPEF from HFREF and from nonfailing individuals, and predict risk of HF incidence in at-risk patient groups, or risk of mortality in HF patients.

In this issue of the *Canadian Journal of Cardiology*, Izumiya et al. succinctly show their findings from cross-sectional measurement of growth differentiation factor-15 (GDF-15) using enzyme-linked immunosorbence assays of serum derived from peripheral blood.[9] GDF-15, a distant member of the transforming growth factor-β superfamily, was a significant predictor of all-cause mortality in a combined cohort of failing and nonfailing patients with diastolic dysfunction, and in a derivative cohort of patients with HFPEF. Interestingly, the cohort of HFPEF patients studied by Izumiya et al. were moderately symptomatic with 10 of 73 patients in New York Heart Association class III HF and only 1 of 73 in New York Heart Association class IV HF. Furthermore, within the HFPEF cohort divided into high and low GDF-15 groups along the median, no differences in therapies emerged that could confound the results. Although small, this study shows rather convincingly that GDF-15 is a powerful prognostic indicator in HFPEF, even in a cohort of patients without advanced heart disease.

Cardiac and other tissues, including adipose, immune, and vascular, secrete GDF-15 in response to various pathological stimuli, such as inflammation, oxidative stress, tissue injury, and adverse remodelling.[15] GDF-15 is a downstream responder to cardiac stressors; it is an indicator of mortality risk in community-dwelling elderly patients without overt heart disease, and in HFREF patients.[16,17] Izumiya et al. suggest that elevation of GDF-15 in HF might represent a compensatory mechanism in response to pathophysiological dysregulation of various signalling cascades.[9] Taking their work together with previous work by Stahrenberg et al., which showed an association between GDF-15 and diastolic dysfunction in HFPEF, and improvements in the accuracy of diagnosing HFPEF when combining GDF-15 and N-terminal pro-B-type natriuretic peptide (NT-proBNP), the association of GDF-15 with both disease progression and combined end points in HFPEF suggests that the compensatory response initiated by the body is insufficient to abrogate disease progression.[7,9] This raises an important question for further research: could recombinant GDF-15 or a GDF-15

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**Table 1.** Pathways implicated in HFPEF identified in biomarker studies

| Biomarker | Physiological role | Association with HFPEF | Study |
|---|---|---|---|
| GDF-15 | Downstream responder to various pathways including inflammation and fibrosis/ECM remodelling | Differentiation from control subjects* and HFREF; diastolic dysfunction and exercise capacity; outcomes | Stahrenberg et al.[7]; Santhanakrishnan et al.[8]; Izumiya et al.[9] |
| MMP-2 | Cleaves collagen type IV; mediates ECM | Differentiation from control subjects* | Zile et al.[10] |
| MMP-8 | Cleaves collagen type I; mediates ECM | Differentiation from control subjects* | Zile et al.[10] |
| TIMP-4 | Mostly cardiac inhibitor of MMPs | Differentiation from control subjects* | Zile et al.[10] |
| PIIINP | Product of collagen type III synthesis | Differentiation from control subjects* | Zile et al.[10] |
| Gal-3 | Mediator of cardiac fibrosis | Incidence; outcomes | Ho et al.[11]; de Boer et al.[12] |
| PTX3 | Responder to cardiac inflammation | Differentiation from control subjects* | Matsubara et al.[13] |
| TNFR1 | One of two major TNF-α receptors; mediates various pathological effects | Incidence | Marti et al.[14] |

ECM, extracellular matrix; Gal, galectin; GDF-15, growth differentiation factor 15; HFPEF, heart failure with preserved (≥ 50%) left ventricular ejection fraction; HFREF, heart failure with reduced (< 50%) left ventricular ejection fraction; MMP, matrix metalloproteinase; PIIINP, collagen type III N-terminal propeptide; PTX3, pentraxin-3; TIMP, tissue inhibitor of MMP; TNF, tumour necrosis factor; TNFR1, TNF-α receptor type 1.

*Control subjects varied between studies: some were healthy individuals, and others were at-risk nonfailing individuals.

receptor agonist be used to supplement the natural response to HFPEF? Targeting the body's natural compensatory response might be a way to achieve more specific therapeutic effects, thereby mitigating potential adverse residual effects. Furthermore, one of the challenges in using GDF-15 as biomarker for HFPEF is the apparent lack of specificity, because patients with HFREF also show elevation in plasma GDF-15 levels and this is correlative with mortality.[17]

A recent reimagination of the pathophysiology of HFPEF places the cardinal elements of the syndrome, left ventricular hypertrophy and diastolic dysfunction, as the end result of a series of pathophysiological events.[6] The suggested site of primary dysregulation is the coronary microvascular endothelium, where the downstream effects of multiple comorbidities frequently associated with HFPEF, such as hypertension, overweight/obesity, and diabetes, culminate to induce oxidative stress. Following the microvascular endothelial dysfunction paradigm, fibrosis/ECM remodelling are consequences of oxidative stress, and GDF-15 secretion is likely a response to the aforementioned stressors and also to the structural changes that occur as a result of these events. Although downstream GDF-15 release in response to some combination of upstream pathophysiological mechanisms seems straightforward, the upstream interplay of various pathways is more complex. Indeed, multiple inputs, such as tumour necrosis factor-α, interleukin-6, pentraxin-3, and secreted soluble interleukin-1 receptor-like protein 1 (ST2), appear to converge on similar effects.[6] It will be worth exploring whether GDF-15 release is mediated in the setting of differential inflammatory signalling, because this might affect its prognostic potential in large and diverse cohorts of patients.

Although the emerging picture of HFPEF is one of a syndrome driven by 2 related entities—inflammation and fibrosis/ECM remodelling—afflicted individuals certainly vary in the proportion of disease for which either major component is responsible. Biomarker studies have shown that multiple molecules share diagnostic and prognostic value with respect to HFPEF. The time is approaching when these molecules might be used to discover the relative contributions of inflammation, fibrosis/ECM remodelling, and other drivers in HFPEF, and to stratify patients accordingly. Importantly, the clinical management of HFPEF might soon rely on this information for a guided approach. The recent work by Izumiya et al. contributes further to the knowledge base on biomarkers in HFPEF covering incidence, progression, and eventual outcomes.[9] As medicine moves away from one-size-fits-all approaches toward individually-tailored therapeutic regimens, the development of effective biomarker panels that contain a cohort of biomarkers to cover the entire natural history of HFPEF will be essential. Furthermore, it is clear that creativity and innovation to develop biomarkers from biochemical tests, imaging, or a combination thereof will be one essential element to allow us climb out of the current therapeutic rut in HFPEF.

With respect to therapeutic options in HFPEF, the setting is presently very bleak, with virtually no options available to health care providers that have been validated by large, double-blind randomized-control trials.[1] Indeed many promising therapies for HFPEF have been terminated after failing in late-phase clinical trials. The issue might be that these therapies target a small subset of the HFPEF population, so their effect is lost among the heterogeneity of the overall population. As evidence mounts that a confluence of inflammation and fibrosis/ECM remodelling is responsible for the pathogenesis of HFPEF in a large subset of the overall population, the work by Izumiya et al. should be another prompt to think creatively about how to manage the growing problem of HFPEF in a society in which the average lifespan is longer and comorbidities more prevalent than ever before.[9] Although Izumiya et al. nicely show that GDF-15 is a predictor of mortality, it now time to address the issue of what meaningful steps can be taken when equipped with prognostic information. With a changing paradigm for HFPEF, new avenues for therapeutic development will reveal themselves. The hope is that some of these might yield more positive results when applied to large, heterogeneous HFPEF cohorts. Ultimately, these novel biomarkers will allow us to better diagnose and prognosticate patients with HFPEF and, most importantly, develop and test novel therapies for HFPEF.

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