What the Dead Can Teach the Living:

The Systemic Nature of Heart Failure with Preserved Ejection Fraction

Running title: *Kitzman et al.; Systemic Nature of HFPEF*

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Heart failure (HF) with preserved ejection fraction (HFpEF) is the most common form of HF. Approximately 90% of new HF cases in older women are HFpEF. Adverse outcomes – exercise intolerance, poor quality-of-life, frequent hospitalizations, and reduced survival – approach those of HF with reduced EF (HFrEF). In contrast to HFrEF, the prevalence of HFpEF is increasing and its prognosis is worsening. Despite the strong public health importance of HFpEF, its pathogenesis is poorly understood. Our lack of understanding of HFpEF and its treatment is punctuated by the fact that 6 large, well-designed, randomized clinical trials and several smaller ones were all neutral on their primary outcomes. The combination of high prevalence and lack of evidence-based treatments makes HFpEF a high-priority topic for research in cardiovascular disease.

A glaring absence among HFpEF studies has been a systematic autopsy-based study. Such studies have become more difficult as autopsy rates have declined with the availability of advanced multi-modality imaging and deep-tissue biopsy techniques. Despite the increasing array of modern research techniques, post-mortem methods continue to be uniquely valuable because of the ability to perform comprehensive, in-depth, detailed examinations of tissues and organs in humans.

In this issue of Circulation, Mohammed and colleagues at the Mayo Clinic fill this critical gap with the first autopsy series of HFpEF. From a tissue registry patiently accumulated over a period of 19 years, their multi-disciplinary team methodically collected and comprehensively analyzed specimens, medical records, electrocardiograms, and echocardiograms from 255 individuals, including patients with pre-mortem diagnosis of HFpEF (n=124) and HFrEF (n=27), and from age-matched case controls who died from non-cardiovascular causes (n=104). Characteristics of the HFpEF patients were relatively similar to
community-based reports, including advanced age and a high prevalence of common comorbidities, including hypertension, diabetes, obesity, and clinical coronary artery disease (CAD).

The array of analyses performed is impressive. The present report focuses on characteristics thought to be typical of HFpEF: cardiac hypertrophy, CAD, and myocardial fibrosis. The authors report a number of key findings. Compared to controls, HFpEF patients had more gross and microscopic cardiac hypertrophy and much higher cardiac weight (though the latter includes all chambers and epicardial fat). CAD was frequent and extensive. HFpEF patients also had greater fibrosis than controls which was similar in degree to HFrEF and independent of CAD severity and hypertension, suggesting that other factors may initiate and promote fibrosis. The most novel finding was that of considerably reduced microvascular density (MVD) which was independent of CAD and in adjusted analyses appeared to account for the increased fibrosis. This novel finding of reduced MVD, or microvascular rarefaction, could be pivotal to HFpEF pathophysiology.

The authors suggest that their findings, particularly microvascular rarefaction, support an over-arching hypothesis for HFpEF pathogenesis: as a result of aging, multiple comorbidities, and probably as yet unidentified factors, there is a systemic pro-inflammatory state that results in systemic arterial and microvascular dysfunction. The study might have provided even more evidence to support this systemic hypothesis if it had examined other tissues and organs for microvascular rarefaction, but unfortunately these were not available since their ambitious project began long before such an hypothesis was originally proposed by Paulus. Nevertheless, this appealing hypothesis is supported by growing evidence, including a recent report that HFpEF patients have increased levels of tumor necrosis factor-α (TNF-α) and its type-2 receptor,
and the latter was elevated even more than in HFrEF.\textsuperscript{4}

One strength of this hypothesis is that it is unifying and incorporates observations that have seemed disparate. These include: the high prevalence of multiple comorbidites and their surprisingly strong impact on outcomes; the failure of cardiac factors alone to fully explain HFpEF symptoms and outcomes; and the strong contributions of extra-cardiac factors, including vascular, kidney, skeletal muscle, and adipose tissue. This hypothesis also helps explain the startling findings that typical HFpEF features can be produced in young hearts perfused with blood from old hearts, and that such features are reversible in old heart and skeletal muscle by perfusing with blood from young animals.\textsuperscript{5}

If HFpEF is a systemic disorder, triggered and advanced by circulating factors, rather than an isolated cardiac disorder, then this opens vistas of new understanding and could promote novel therapeutic approaches. For instance, some studies have indicated that exercise intolerance - the primary symptom in chronic HFpEF - is due to cardiac factors.\textsuperscript{6} Other studies indicate peripheral factors, such as vascular and skeletal muscle, are responsible.\textsuperscript{7} Still other studies indicate a combination of heart, vascular, and skeletal muscle abnormalities are responsible;\textsuperscript{8} which would be consistent with a systemic disorder. If a systemic process is responsible, perhaps mediated by circulating factors, then adverse effects on striated muscle in both cardiac and skeletal muscle compartments would be expected. Indeed, the authors’ current finding of microvascular rarefaction in cardiac muscle nicely parallels a recent report showing nearly 50% lower capillary density in thigh muscle of HFpEF patients compared to controls which was significantly correlated with their severe exercise intolerance (\textbf{Figures 1-2}).\textsuperscript{9}

As the authors state, autopsy studies can overestimate the prevalence of a disorder or a feature of disease compared to living population samples. The authors found 76% of HFpEF
patients had LV hypertrophy, about 50% higher than reported from the Olmsted County population and the I-PRESERVE and TOPCAT trials, and much greater than the 8% reported from a recent clinical trial of well-characterized HFpEF patients. In the population-based CHS study, there was no difference in LV mass in elderly HFpEF compared to controls with hypertension alone. The degree of increased fibrosis in the current report, while at the high end of reports from biopsy and imaging studies, was relatively modest compared to controls, and the authors suggest was likely insufficient to account for cardiac dysfunction in HFpEF. Although prevalence of CAD in this report was similar to one catheterization based study, the latter represented selected patients. Further, cohorts of symptomatic HFpEF patients have been reported where CAD was excluded clinically. The totality of data suggest that neither LV hypertrophy, CAD or perhaps even fibrosis are unique to - or required for - HFpEF, supporting the systemic hypothesis and helping explain clinical trial results where these were targeted.

What are the therapeutic implications of the investigators’ findings of cardiac hypertrophy, fibrosis, and CAD? The pharmacological agents clinically tested in HFpEF to date and found neutral on their primary outcomes (ACE inhibitors, angiotensin receptor antagonists, aldosterone inhibitors, and collagen cross-link breakers) had proven ability to ameliorate LV hypertrophy, fibrosis and other cardiac abnormalities typically found in HFpEF. Regarding the findings of occlusive CAD, studies indicate that: clinically-evident, acute coronary ischemia may not be the key trigger for acute decompensation in HFpEF and ejection fraction doesn’t decline during an acute episode; revascularizating coronary stenoses has little effect on preventing recurrence of acute HFpEF; and severe exercise intolerance occurs in chronic HFpEF when clinical coronary ischemia has been excluded. Interestingly, exercise training - the only intervention to date definitively proven to improve exercise intolerance in chronic HFpEF -
appears to do so primarily via peripheral, non-cardiac mechanisms.\textsuperscript{15}

The investigators’ novel, potentially pivotal finding of microvascclar rarefaction has several intriguing therapeutic implications. If this is triggered by systemic inflammation, then a promising signal is the novel agent LCZ696, an angiotensin receptor neprilysin inhibitor, which is currently being tested in a large clinical trial. This agent appears to reduce TNF-\(\alpha\) levels and this correlates with improvements in cardiac features of HFpEF.\textsuperscript{16} Another potential signal is that statins may modify systemic inflammation and stabilize endothelium.\textsuperscript{17} Several current clinical trials are testing novel agents to regenerate skeletal muscle in elderly with multiple comorbidities and sarcopenia; if successful, these could inform new approaches to HFpEF. Other novel approaches will likely emerge if evidence supporting the systemic hypothesis continues to accumulate.

Microvascular rarefaction in HFpEF could also be potentially addressed with non-pharmacological interventions. In skeletal muscle, degeneration/regeneration appears to be under neural, autonomic control. A recently launched trial adapts this principle to test whether a novel vagal stimulation device can produce anti-apoptosis, anti-inflammatory, and improved remodeling in cardiac muscle in HFrEF.\textsuperscript{18} Another potential avenue for intervention derives from the facts that excess adipose tissue is pro-inflammatory, and elderly HFpEF patients have abnormal adipose infiltration into skeletal muscle which is associated with their severe exercise intolerance.\textsuperscript{19} Obesity is associated with substantial, widespread microvascular rarefaction as a result of both accelerated degeneration and impaired regeneration.\textsuperscript{20} Approximately 85\% of elderly HFpEF patients are overweight or obese, and the HFpEF epidemic has largely paralleled the obesity epidemic. In obese non-HFpEF patients, weight loss interventions improve LV hypertrophy, hypertension, and diastolic, vascular, and skeletal muscle function and exercise
performance, but have not been examined in HFpEF.

We offer additional perspective to help reassure cardiologists uncomfortable with a paradigm conceptualizing the most common form of “heart failure” as anything other than a purely cardiac disorder. Strong evidence indicates that even classic HFrEF, particularly in elderly, is a systemic process, involves multiple organ systems, and is strongly impacted by comorbidities, including obesity. HFpEF, like other geriatric syndromes, remains a true, distinct disorder; it is not merely a collection of multiple comorbidities with a dash of aging thrown in. Also, the heart remains a pivotal part of the equation. As the organ that is not allowed to rest, symptoms quickly develop when its reserve capacity is impaired. Thus, the heart may serve as the ‘canary-in-the-coal-mine’ when the perfect storm of events colludes to bring about HFpEF. As such, cardiologists will still lead the assault on HFpEF. We have a proud tradition of going outside our comfort zone to tackle challenging disorders, as was done during development of thrombolytic therapy for acute MI. Finally, HFpEF patients will be grateful for symptom relief and improved quality-of-life, regardless of whether this derives from an innovation that doesn’t seem cardiocentric.

So, what can the dead teach us about HFpEF? That comorbidities, heterogeneity and multi-factorial etiologies are the rule rather the exception in disorders of the elderly. And that embracing these concepts under the unifying hypothesis of a systemic disorder can provide needed insights and facilitate progress toward conquering, or at least taming, this stubborn but important age-related disorder.

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References:


Figure Legends:

**Figure 1.** Capillary density (capillary-to-fiber ratio) from thigh muscle biopsy in elderly patients with HFPEF and age-matched control subjects. Adapted from Kitzman et al; Am J Physiol Heart Circ Physiol 2014;306:H1364-1370.

**Figure 2.** Relationship of capillary density (capillary-to-fiber ratio) with peak exercise O2 uptake (V\textsubscript{O}\textsubscript{2}), an objective measure of exercise capacity, in older patients with HFPEF (■) and age-matched control subjects (▲). From Kitzman et al\textsuperscript{9} with permission.
Figure 1
Figure 2

Peak VO₂ (ml/kg/min)

$r = 0.59$

$p = 0.001$
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