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.1 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.2 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.

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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 multimodality imaging and deep-tissue biopsy techniques. Despite the increasing array of modern research techniques, postmortem 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 colleagues3 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 multidisciplinary team methodically collected and comprehensively analyzed specimens, medical records, electrocardiograms, and echocardiograms from 255 individuals, including patients with premortem diagnosis of HFpEF (n=124) and HFrEF (n=27), and from age-matched case controls who died of noncardiovascular 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 mellitus, 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. In comparison with controls, HFpEF patients had more gross and microscopic cardiac hypertrophy and much higher cardiac weight (although the latter includes all chambers and epicardial fat). CAD was frequent and extensive. HFpEF patients also had greater fibrosis than controls that 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 that was independent of CAD and in adjusted analyses appeared to account for the increased fibrosis. This novel finding of reduced microvascular density, or microvascular rarefaction, could be pivotal to HFpEF pathophysiology.

The authors suggest that their findings, particularly microvascular rarefaction, support an overarching hypothesis for HFpEF pathogenesis: as a result of aging, multiple comorbidities, and probably as yet unidentified factors, there is a systemic proinflammatory 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 because 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 and its type 2 receptor, and the latter was elevated even more than in HFrEF.4

One strength of this hypothesis is that it is unifying and incorporates observations that have seemed disparate. These observations include the high prevalence of multiple comorbidities 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 extracardiac 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.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 attributable to cardiac factors.6 Other studies indicate that peripheral factors, such as vascular and skeletal muscle, are responsible.7 Still other studies indicate that a combination...
of heart, vascular, and skeletal muscle is responsible,\(^8\) 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 \(\approx 50\%\) lower capillary density in the thigh muscle of HFpEF patients in comparison with controls which was significantly correlated with their severe exercise intolerance (Figures 1 and 2).\(^9\)

As the authors state, autopsy studies can overestimate the prevalence of a disorder or a feature of disease in comparison with living population samples. The authors found that 76% of HFpEF patients had left ventricular (LV) hypertrophy, \(\approx 50\%\) higher than reported from the Olmsted County population and the Irbesartan in Heart Failure With Preserved Systolic Function (I-PRESERVE) and Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trials, and much greater than the 8% reported from a recent clinical trial of well-characterized HFpEF patients.\(^10\) In the population-based Cardiovascular Health Study, there was no difference in LV mass in elderly HFpEF patients in comparison with controls with hypertension alone.\(^11\) The degree of increased fibrosis in the current report, although at the high end of reports from biopsy and imaging studies, was relatively modest in comparison with controls, and the authors suggest that it was likely insufficient to account for cardiac dysfunction in HFpEF. Although the prevalence of CAD in this report was similar to 1 catheterization-based study, the latter represented in HFpEF. Although the prevalence of CAD in this report was similar to 1 catheterization-based study, the latter represented in HFpEF. Although the prevalence of CAD in this report was similar to 1 catheterization-based study, the latter represented in HFpEF.

The totality of data suggest that neither LV hypertrophy, nor 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?\(^3\) The pharmacological agents clinically tested in HFpEF to date and found neutral on their primary outcomes (angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, aldosterone inhibitors, and collagen cross-link breakers) had a 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 the ejection fraction does not decline during an acute episode;\(^13\) revascularizing coronary stenoses has little effect on preventing the recurrence of acute HFpEF;\(^1\) and severe exercise intolerance occurs in chronic HFpEF when clinical coronary ischemia has been excluded.\(^12\) Interestingly, exercise training, the only intervention to date definitively proven to improve exercise intolerance in chronic HFpEF, appears to do so primarily via peripheral, noncardiac mechanisms.\(^15\,15\)\(^a\)

The investigators’ novel, potentially pivotal finding of microvascular 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 tumor necrosis factor-\(\alpha\) levels, and this finding correlates with improvements in cardiac features of HFpEF.\(^16\) Another potential signal is that statins may modify systemic inflammation and stabilize endothelium.\(^17\) Several current clinical trials are testing novel agents to regenerate skeletal muscle in elderly patients 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 nonpharmacological 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 antiapoptosis, anti-inflammatory, and improved remodeling in cardiac muscle in HFpEF.\(^18\) Another potential avenue for intervention derives from the facts that excess adipose tissue is proinflammatory, and elderly HFpEF patients have abnormal adipose infiltration into skeletal muscle that is associated with their severe exercise intolerance.\(^19\) Obesity is associated with substantial, widespread microvascular rarefaction as a result of both accelerated degeneration and impaired regeneration.\(^20\) 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

Figure 1. Capillary density (capillary-to-fiber ratio) from thigh muscle biopsy in elderly patients with HFpEF and age-matched control subjects. HFpEF indicates heart failure with preserved ejection fraction. Adapted from Kitzman et al\(^9\) with permission of the publisher. Copyright ©2014, the American Physiological Society.

Figure 2. Relationship of capillary density (capillary-to-fiber ratio) with peak exercise \(\dot{V}O_2\), an objective measure of exercise capacity, in older patients with HFpEF (◼) and age-matched control subjects (▲). HFpEF indicates heart failure with preserved ejection fraction. Reprinted from Kitzman et al\(^9\) with permission of the publisher. Copyright ©2014, the American Physiological Society.
diastolic, vascular, and skeletal muscle function and exercise performance, but have not been examined in HFpEF.

We offer an 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 patients, 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 the heart’s 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 the development of thrombolytic therapy for acute myocardial infarction. Finally, HFpEF patients will be grateful for symptom relief and improved quality of life, regardless of whether this derives from an innovation that does not seem cardiocentric.

So, what can the dead teach us about HFpEF? That comorbidities, heterogeneity, and multifactorial etiologies are the rule rather the exception in disorders of the elderly population. 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

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