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Einstein, the blind men, and the elephant: making sense of heart failure with preserved ejection fraction

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Nearly 30 years ago, Milton Packer published an editorial entitled, “How should we judge the efficacy of drug therapy in patients with chronic congestive heart failure? The insights of six blind men (1).” The title refers to the ancient parable of six blind men who attempt to define what an elephant is like by describing the part of the animal they are able to feel; to the man holding the leg, the elephant is a thick column, to the man holding the tail, a rope. In Dr. Packer’s version, the “blind men of heart failure” evaluate symptoms, clinical fluid retention, noninvasive measures of left ventricular function, invasive hemodynamic evaluation, evaluation of functional capacity, and survival. All are viewed as distinct but related endpoints worthy of consideration; caution is advised towards overreliance on any one aspect as representative of the whole. While this editorial was written in reference to heart failure with reduced ejection fraction, the analogy may be even more relevant to heart failure with preserved ejection fraction (HFpEF).

One of the first patients I saw as a cardiologist was a 78-year old woman with a resilient spirit, but a litany of health problems including coronary artery disease, obesity, anemia, diabetes mellitus, hypertension, chronic kidney disease, sleep apnea, and polymyalgia rheumatica. Over the year prior to her visit with me in clinic, she had been hospitalized five times for decompensated HFpEF. The most recent episode had occurred three hours after her family’s Thanksgiving dinner, when she developed the rapid onset of pulmonary edema, resulting in emergent intubation in her own living room and a five-day intensive care unit stay.

This situation led to several questions, most importantly from my patient, who asked whether what she had eaten for supper had contributed to her terrible ordeal. I admitted that I didn’t know, but her question inspired my ongoing efforts to understand the connections between dietary patterns and the progression of HFpEF. With diuresis, blood pressure control, frequent clinic visits, and telemanagement, my patient no longer suffered hospitalizations for heart failure. Despite this seeming success, her overall quality of life remained quite poor. I wondered how her many comorbidities contributed to her heart failure, and why other patients with similar illness burden never develop HFpEF. Her overall

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level of exercise intolerance and exhaustion was striking – how much of this frailty was due to heart failure itself, and how much was related to deconditioning, chronic pain, or other causes?

These questions continued a process that started during my internal medicine residency at Columbia University 15 years ago. At the time, I was struggling to decide between geriatrics and cardiology for fellowship training. My early clinical opportunities had instilled an affinity for taking care of older patients. I liked untangling the complexity of their conditions and how they intersected with each other, and how doing so could improve the functional aspects and overall quality of a patient's life. However, my interest in cardiovascular physiology cultivated via undergraduate engineering studies, medical school courses, and my cardiac intensive care unit rotations clearly pointed me toward a career in cardiology. Amid my confusion, I was told that I should meet with Mat Maurer, a junior faculty clinical researcher and “geriatric cardiologist.”

I was unaware that such a field even existed, and at the time was pretty sure I didn't want to be a researcher. As the director of the Clinical Cardiovascular Research Laboratory for the Elderly at Columbia, Mat was using classical cardiovascular physiology techniques to explore the possibility that “diastolic” heart failure was not quite so straightforward as conventionally assumed (2,3). It didn't take long for my fate to be sealed - I was energized by Mat's enthusiasm for confronting difficult questions, intrigued by the many gaps in knowledge, and compelled by the unmet treatment needs presented by millions of patients with HFpEF. These same motivations still drive researchers in the field today, as this major and growing public health threat (4) remains without definitive therapy.

Complex insights from a simple foundation

The last two decades of clinical research in HFpEF have been marked by the largely disappointing results of randomized clinical trials employing neurohormonal blockade, so successful in heart failure with reduced ejection fraction. At least some trials suffered due to enrollment of participants with widely varying characteristics and prognosis – some of whom may not have had HFpEF at all (5). The importance of standardized diagnostic criteria for HFpEF has become clear – as have some of the challenges in establishing such a framework. Diagnostic algorithms for HFpEF that require evidence of increased left heart filling pressures, cardiac structural remodeling, and/or elevated natriuretic peptide levels (6) have improved specificity. However, patients with markedly elevated filling pressures do not always have increased natriuretic peptide levels (7), the prevalence of cardiac structural abnormalities such as left ventricular hypertrophy varies widely depending on the population studied (8,9), patients with negative echocardiographic signs (e.g. normal or equivocal mitral E/e' ratio) may have increased filling pressures upon invasive analysis (10), and an appreciable fraction have normal filling pressures at rest that only increase during exercise (11,12). Just from these observations alone, it seems evident that HFpEF is not the same disease in all patients (13), and that deeper physiologic understanding is needed.

As Albert Einstein once said, “It can scarcely be denied that the supreme goal of all theory is to make the irreducible basic elements as simple and as few as possible without having to

surrender the adequate representation of a single datum of experience (14).” This statement is often paraphrased as, “Make things as simple as possible, but no simpler.” Following this wise advice, additional insight has come from breaking down the cardinal manifestation of HFpEF, exercise intolerance, into its foundational components. The aerobic fitness of an individual can be expressed in terms of peak oxygen consumption, or VO_2 peak, achieved during exercise. In patients with HFpEF, VO_2 peak is markedly impaired compared with age-matched controls (15,16). The Fick principle defines oxygen consumption as the product of ventricular stroke volume (SV), heart rate (HR), and arteriovenous oxygen concentration difference ($A-V_{\text{diff}} \text{O}_2$), i.e. $\text{VO}_2 = \text{SV} \times \text{HR} \times A-V_{\text{diff}} \text{O}_2$. This straightforward equation expresses the possibility that exercise intolerance could relate to abnormalities in any or all of these three parameters.

Following Dalane Kitzman’s seminal observation that patients with heart failure and normal left ventricular ejection fraction failed to increase left-ventricular end-diastolic volume during exercise (17), research first focused on ventricular diastolic dysfunction as the primary limitation to stroke volume and cardiac output during physical activity. Noting the high prevalence of hypertension in patients with HFpEF, in 2003 David Kass and colleagues demonstrated that vascular stiffening reduced systolic ventricular reserve function in HFpEF, identifying another mechanism for limiting stroke volume during exercise (18). In 2006, work by Barry Borlaug and others revealed chronotropic incompetence, i.e. failure to increase heart rate commensurate to the demands of activity (19). Additional work using contemporary techniques has validated the importance of diastolic dysfunction, impaired systolic reserve, arterial stiffness, and chronotropic incompetence in limiting cardiac output and contributing to exercise intolerance in patients with HFpEF (15,20,21).

With these data in mind, in 2011 Dalane Kitzman’s group reexamined the determinants of VO_2 peak during bicycle exercise. As per their prior work, they hypothesized that reduced VO_2 peak in patients with HFpEF would be due to blunted increase in end-diastolic volume, and hence stroke volume and cardiac output. Somewhat to their surprise, they found that the strongest determinant of VO_2 peak was reduction in $A-V_{\text{diff}} \text{O}_2$ (22), an observation later confirmed by Gregory Lewis and colleagues (16). This suggests that the key deficiency in at least some patients with HFpEF is impairment in the delivery of oxygen to metabolizing muscles or in the ability of those muscles to utilize the oxygen they receive.

In 2013, Walter Paulus and Carmen Tschöpe proposed a new paradigm for the pathophysiology of HFpEF, in which multiple pro-oxidant comorbid conditions cause coronary microvascular inflammation and dysfunction (23). This exciting and potentially unifying premise has since been strongly supported by data from endomyocardial biopsies demonstrating vascular inflammation and autopsy specimens showing cardiac capillary rarefaction in patients with HFpEF (24,25). However, microvascular function and capillary density are also abnormal in skeletal muscle (26–28), which likely contributes to impaired oxygen diffusion and extraction (16). Skeletal muscle biopsies demonstrate increased intramuscular fat and fewer type I “slow-twitch” oxidative muscle fibers compared with age-matched controls (28). In addition to these differences in skeletal muscle quality, the number and oxidative capacity of skeletal muscle mitochondria are comparatively reduced in patients with HFpEF (29). Viewed through this lens, HFpEF appears to be a global

microvascular and metabolic disorder rather than a primary cardiac abnormality. It is no accident that exercise has been the most consistently beneficial therapy for HFpEF in randomized controlled trials (30–32).

Phenotyping in HFpEF: from big data to the patient in front of you

Recently, it has been proposed that disease phenotyping is needed to match patients with HFpEF to the appropriate treatment strategy (33). Patterned after previous work in other fields such as oncology, several groups have used machine learning techniques to group and characterize HFpEF patients. Sanjiv Shah and colleagues performed an unbiased analysis of 67 clinical variables in patients with HFpEF from a large clinical registry. They found that three pheno-groups optimally described the prognosis of HFpEF with respect to death and cardiovascular hospitalization (34). Using similar techniques, David Kao and co-authors have extended prognostic phenogrouping to patients previously enrolled in large HFpEF clinical trials (35). These important “big data” observations may eventually improve selection of high-risk patients with HFpEF for clinical trials focused on mortality and cardiovascular hospitalization (33). However, it is worth noting that cardiovascular hospitalization rates are lower and death is more commonly due to non-cardiovascular causes in HFpEF than in heart failure with reduced ejection fraction (36,37). These observations likely relate to the higher comorbidity burden found in patients with HFpEF, which also manifests in phenomapping studies. For example, younger obese patients with HFpEF who have few other illnesses have a better prognosis than older patients with diabetes, anemia, muscle wasting, and renal insufficiency (34,35).

While this makes intuitive sense, how should I apply these findings to my patient with HFpEF, who had all of these risk factors (and more) predicting death and readmission? Moreover, was this classic heart failure trial endpoint the most meaningful outcome for her? After my patient’s initial crisis of respiratory failure was resolved, her primary goals were to feel better and remain functional on an everyday basis. In this way, she was similar to many other elderly patients with chronic disease. This point was reinforced by a recent study in which only 7% of elderly patients with severe aortic stenosis considering transcatheter aortic valve replacement (TAVR) defined their most important goal as to live longer. In contrast, nearly half primarily wanted to recover the ability to do a specific activity, such as dancing or gardening, 30% felt that maintaining independence was most critical, and the remaining 15% of patients hoped to reduce their overall symptom burden (38).

Providing care to multi-morbid older adults with HFpEF demands similar consideration of such concerns. Cardiologists are accustomed to making decisions guided by robust evidence gained from large randomized trials. The prevailing attitudes towards HFpEF have historically been dismissive (39) and/or fatalistic, “it’s boring, and there isn’t any treatment for that.” This viewpoint may be changing gradually, with editorials written by leaders in the field advocating physiological phenotyping of HFpEF to guide treatment strategies (40,41). The most important phenotyping may begin when you shake their hand – how’s their grip strength (42)? Can they get up from a chair and climb onto your exam table (43)? In those who are able to perform it, I learn a lot from a simple test: “Walk with me until you get tired or out of breath.” How quickly do they walk (42,44)? Why do they stop walking- dizziness?

Balance? Tired legs? Shortness of breath? What is their blood pressure and heart rate response – do they have exaggerated systolic hypertension (16)? Chronotropic incompetence (15)? In conjunction with an assessment of volume status by history and examination, this simple evaluation of hemodynamic status and submaximal physical function goes a long way towards identifying the predominant mechanisms that are making a patient with HFpEF feel poorly, and can help set the expectations for treatment. Further information can then be incorporated from echocardiography to assess pulmonary pressures (45), right heart impairment (46), and left ventricular systolic (47) and diastolic (48) dysfunction. If the patient is able (and willing) to perform them, exercise VO₂ testing and right heart catheterization (11) can add extremely helpful context to physiological phenotyping.

Over the past few months in our HFpEF clinic, I have recommended exercise regimens and dietary changes; I have used loop diuretics frequently and mineralocorticoid antagonists judiciously. I have also treated patients using verapamil for systolic mid-cavitary left ventricular obstruction, ranolazine for microvascular coronary disease, digoxin and sildenafil for pulmonary hypertension with right ventricular dysfunction, beta-blocker reduction for chronotropic incompetence, ivabradine for inappropriate sinus tachycardia, and diflunisal for transthyretin amyloidosis. Is this evidence-based treatment in the traditional sense? Definitely not. Is this targeted therapy based on physiological phenotyping that helps patients? I think that it is. I also hope that I am convincing our general cardiology and advanced heart failure fellows that HFpEF is not boring! On the contrary, each patient with HFpEF requires a nuanced, multi-layered, and integrative assessment from most or all of Dr. Packer's six blind men. I suspect this will remain true regardless of any advances in the years ahead.

The road ahead in HFpEF: embracing complexity

The recent Nitrate's Effect on Activity Tolerance in Heart Failure with Preserved Ejection Fraction (NEAT-HFpEF) trial did not show benefit for isosorbide mononitrate, but its emphasis on assessing and improving daily activity and quality of life represented a major shift in trial design for HFpEF (49). Inorganic nitrates/nitrites, on the other hand, acutely improve exercise hemodynamics in HFpEF (50,51), and interestingly also skeletal muscle power in patients with heart failure and reduced ejection fraction (52). Longer-term studies are currently in progress, again with focus on functional endpoints. Diet-induced weight loss appears to benefit morbidly obese patients with mild HFpEF (30), but it is unclear whether improvement relates to changes in fat distribution, dietary nutritional quality, or metabolic efficiency (53,54). It is also unknown whether weight loss would benefit patients with more severe HFpEF, in particular more frail obese patients with a greater degree of sarcopenia. The intersection between frailty and the prognosis and progression of HFpEF is not completely defined, and substantial research opportunities exist in studying shared mechanisms of these two age-related phenomena (55,56). Insights gained from this work should inform what may be the most important question, the true elephant in the room: why do people develop HFpEF in the first place? These inherently multidisciplinary efforts require "embracing [the] complexity" (57) of HFpEF, and incorporate many of the principles, assessment techniques, and translational research aims of geriatric cardiology (58,59).

In most versions of the tale of the blind men and the elephant, the six men devolve into vehement disagreement, each certain that his interpretation comes closest to explaining the whole. This warns us as clinicians not to focus too intently on any one aspect of HFpEF without considering the whole picture presented by the patient. This ending also provides an allegory for the history of HFpEF research, which until recently has been divided into camps strongly supporting or passionately opposed to particular mechanisms, or even the existence of HFpEF itself (39). A more hopeful interpretation of the parable was beautifully expressed by Rumi, a 13th century Persian scholar, jurist, and mystic, in the conclusion of his poem *The Elephant in the Dark*:

Each of us touches one place
and understands the whole that way.
The palm and the fingers feeling in the dark
are how the senses explore the reality of the elephant.

If each of us held a candle there,
and if we went in together, we could see it.

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