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What's EF got to do, got to do with it?

David A. Kass, M.D.

Johns Hopkins University School of Medicine, Division of Cardiology, Baltimore, MD

In the beginning there was heart failure (HF). Patients had fatigue, dyspnea, lung and dependent-limb edema, and big-weak hearts. When hearts were first imaged in the 1930's, we learned they normally eject about 2/3 of their filling volume, and ejection fraction was born. As HF patients had increased EDV but normal or reduced SV, EF was lower and became a marker for HF. While there were also undoubtedly patients with HF symptoms but non-dilated hearts and so normal or even high EFs, we mostly ascribed that to something else. But in the 1960's, the idea caught on that HF could occur even in patients without cardiac dilation and they often had EFs that were not reduced. Many had ischemic or hypertrophic-hypertensive heart disease and were quite elderly. As systolic function seemed intact but diastole impaired, the syndrome soon became diastolic heart failure. Then we learned a lot more was going on, and that diastolic dysfunction was common in many elderly adults with similar co-morbidities, but this did not mean they had HF. We needed a better name for this syndrome and after some sparing, by 2005 we settled on HF with preserved EF – *aka* HFpEF.

We called the syndrome HFpEF not because this implied a pathophysiology, but because it simply described two main features – patients have symptoms of HF and an EF that is not reduced. We now know HF symptoms cannot all be blamed on the heart, as HFpEF also involves pulmonary, renal, skeletal muscle, vascular, metabolic (obesity) and other system dysfunction. That the first HFpEF therapy to successfully reduce cardiovascular death/hospitalization turns out to be a diabetes drug (SGLT2 inhibitor) not previously known to modulate the heart, says a lot. Once we settled on HFpEF, original HF (EF<35%) needed a new name – so it became HF with reduced EF (HFrEF). Patients in the donut hole got a name too - HFmrEF (mr for mid-range). But remember, pEF was never meant to suggest anything more than it's not-rEF.

It's with this background that I find recent efforts to turn EF into a HFpEF biomarker puzzling. In this analysis, HFpEF patients are further divided into those with more (>60–65%) versus less preserved (50–60%) EF, suggesting they have different heart diseases in need of different precision-guided approaches[1]. This seems odd given EF is a rather imprecise assessor of heart function, being sensitive to contractility but also to vascular resistance (declines at higher afterload), heart rate (lower with faster rates), and preload. The

Address Correspondence: David A. Kass, M.D., Division of Cardiology, Johns Hopkins University, Ross 858, 720 Rutland Avenue, Baltimore, MD 21205, 410-955-7153, dkass@jhmi.edu, @dkassjhu.

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preload dependence in HF stems from the fact that while SV declines with EDV (Starling's Law), SV gets to zero first. Furthermore, cardiac output and heart rate both scale to body size and are neuro-hormonally regulated to achieve a mean arterial pressure of ~90 mmHg at the base of the brain, and diastolic pressures >75–80 mmHg to provide adequate coronary perfusion. This constrains them, and we see this in our patients with HF who often have resting SV close to normal until severe failure sets in. Reserve CO is another story, but here we are discussing resting parameters. If SV is more conserved, then the primary determinant of EF becomes EDV. This is certainly true for HFrEF, as a low EF mostly reflects chamber dilation and not always muscle function. For example, it falls in hearts with large infarct scars but otherwise normal residual muscle just as with diffuse cardiomyopathy. I am not saying EF only reflects heart size or is useless to distinguish depressed versus non-depressed function; however, I would not go too much further.

Given the impact of heart size on EF, it is not surprising that HFpEF patients with higher EF have smaller hearts and are more often women (women have smaller hearts)[1]. HFpEF patients with EFs closer to 50% have larger hearts. This also influences cardiac mechanics and must be kept in mind when interpreting such data. For example, pressure-volume analysis shows higher end-systolic and end-diastolic elastances suggesting higher contractility and diastolic stiffness in those with higher EFs and predicts different preload and afterload responses[1, 2]. However, both elastances vary inversely with chamber volume so will be higher in the EF>60% HFpEF group with smaller EDV. That does not necessarily reflect major pathobiological differences; a perfectly normal smaller heart would also have higher values. The majority of HFpEF patients are now obese and this imposes a volume load so having a smaller ventricle is probably a disadvantage. However, I'd suggest this is best solved by reducing obesity and not enlarging the heart.

There are HFpEF patients with truly supranormal EF>75%, but they are a different group generally with more hypertension, hypertrophic disease, and LV cavity obliteration. This was once a more common phenotype, and in our 2003 study, we reported on such patients that had systolic pressures of nearly 170 mmHg, had higher EFs, end-systolic and end-diastolic elastances, and load-induced cardiac reserve limitations[3]. This phenotype is much less prevalent today being taken over by obesity. Still the same hemodynamic principles apply. According to the AHA, a normal EF is between 50–70%, so I would pause before claiming those with EF>60% have a particularly maladaptive form of HFpEF. Also, metrics unaffected by chamber size, such as the slope of a stroke work-EDV relation for contractile function or diastolic stress/strain ratio could help dissect out the role of chamber size.

Taking a step back, it is worth remembering why we called the syndrome HFpEF in the first place. It was not because EF was considered so insightful but because it indicated you did not have rEF. Having pEF does not even mean your myocyte contractile function is "preserved", as we reported in obese HFpEF patients with EFs >60% yet very depressed calcium-dependent tension in skinned myocytes from their ventricular septum[4]. While HFrEF and HFpEF certainly exhibit differences in their transcriptome, they also have many similarities[5], and more pertinent to this commentary, EF does not identify transcriptomic or sarcomere-function subgroups among HFpEF patients[4, 5]. In ongoing work, we do not see EF distinguishing metabolic or proteomic differences either. However, I believe molecular/

cellular features rather than EF are more likely to lead to effective therapeutic targets. In this respect, I would make a plug for more data from relevant tissues and not just blood. Biomarkers in blood are like testing for COVID-19 in wastewater; you know something is going on but not necessarily where or why.

The goal of a name is to capture the essence of something. In this respect, HFpEF has issues, since we now know EF is not so preserved on exertion, that many factors contribute to HF symptoms, and even profound myocyte dysfunction can co-exist despite pEF. Subdividing HFpEF by EF ranges is mostly telling us what is predicted by cardiovascular models, but not too much about the underlying biology. I believe we need more insight into the latter to discover therapies that will work. Perhaps we also need a less distracting name. Before HFpEF became accepted, I had borrowed from Steven Spielberg, referring to Heart Failure of the 1st kind (obviously systolic), 2nd kind (obviously diastolic) or 3rd kind (not obviously either – *aka* HFpEF). Admittedly, this may be a tough name to convey to our patients, but it would solve the EF problem.

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