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# HFpEF, is it more than just the sum of its parts?

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This issue of our journal focuses on the highly topical subject of heart failure with preserved left ventricular ejection fraction (HFpEF). It is clear from congresses and journals that HFpEF's popularity is on the rise. This is hardly surprising given that its high prevalence, morbidity, and mortality combine with a lack of effective therapy. This combination provides the "perfect storm," whipping up academic and commercial interest. Against such backdrop, the articles in this issue provide a balanced view of this field, which often attracts polarized opinion.

A good place to start is the "basic and clinical perspective" provided by Ajay Shah and Philip Chowienczyk. This article highlights the varied pathologies that drive HFpEF and makes the point that current guidelines recommend nothing other than the treatment of comorbidities because there is no clear mechanism of disease causation. Without a dominant mechanism driving disease, it's difficult to create animal models that recapitulate the phenotype(s) seen in patients. The question is Why are patients with HFpEF so heterogeneous?

One of the key causes of heterogeneity in HFpEF is the difficulty in diagnosing this condition. This issue is tackled by Thomas Marwick in his article on how to diagnose HFpEF. The article makes the point that there are two main modes by which patients present: with acute pulmonary edema in the acute care setting and with more insidious disease with progressive breathlessness and fatigue in the ambulatory care setting. Acute presentation with documented pulmonary edema that rapidly resolves with diuresis provides enhanced diagnostic specificity, provided that other triggers such as dynamic mitral regurgitation and tachyarrythmia are excluded. The problem lies in those who present with chronic symptoms, which constitutes the majority of patients. Here, the diagnosis relies on demonstrating abnormal myocardial relaxation; however, as Thomas Marwick discusses, current noninvasive methods lack specificity because with age many of the measured parameters change in the same direction as in HFpEF. Consequently, differentiating HFpEF from "healthy" aging is more art than science. Newer echocardiographic techniques that use speckle tracking to measure myocardial strain may offer improvements in specificity, as may other imaging modalities.

The article by James Moon and colleagues discusses some of these newer imaging techniques but focuses on the use of cardiac magnetic resonance imaging (cMRI). The advantage of cMRI is its ability to quantify myocardial extracellular volume through use of contrast agents and native T1. The above-mentioned "basic and clinical perspective" article by Ajay Shah and Philip Chowienczyk discusses the physiology of diastole, which is divided into an active phase determined by actin-myosin crossbridge detachment and a passive phase determined by the restoration

of elastic components within the myocardium that were distorted during systole. Diffuse myocardial fibrosis will alter passive myocardial relaxation. Thus, as argued by James Moon, cMRI is one of the few techniques that can actually provide some insight into the pathology causing abnormal relaxation. This ability to look "upstream" also enables cMRI to raise the suspicion of senile amyloid (caused by myocardial deposition of wild-type transthyretin), which is almost certainly underdiagnosed and for which specific treatments may soon be available.

This focus on passive relaxation is complemented by the Hot Topics article by Vasco Sequeira and Jolanda van der Velden, which concentrates on abnormal active relaxation. The underlying premise is that healthy relaxation requires fast detachment of the actin-myosin crossbridges and that this in turn is energetically demanding, relying on adenosine triphosphate (ATP) to drive the sarcoplasmic reticulum calcium ATPase to clear the systolic calcium transient and also to replace adenosine diphosphate (ADP) on myosin. Effectively, both these processes are dependent on a high concentration of ATP but also on a low concentration of ADP (ATP/ADP ratio). Thus, a high concentration of ADP pollutes the fuel driving contraction, fostering the concept that the failing heart is an engine running on bad fuel and that this manifests as impaired relaxation. This raises the obvious question of what can be done to remedy the situation.

The article by Yury Lopatin summarizes the new European Society of Cardiology (ESC) heart failure guidelines and points out that trimetazadine is now given a class IIbA recommendation for use in the treatment of angina in heart failure patients on a β-blocker or who are unable to tolerate a β-blocker. Mirroring the Hot Topics article, Yury Lopatin postulates that trimetazadine may have additional benefits on the heart failure process itself by increasing the efficiency of conversion of ADP to ATP.

As pointed out by most of the contributors, there are no specific therapies that alter mortality in HFpEF. This topic is discussed in detail in the article by Sebastian Ewen and Michael Böhm who summarize all the main past and forthcoming trials of drugs and devices in HFpEF. The article makes sobering reading because it highlights the substantial investment already made in HFpEF, often treading a path that has proven successful in HFrEF. Although ongoing studies may provide a light at the end of the tunnel; the question still remains, why have past trials failed? In this issue, I have attempted to answer this question in my article entitled "Treatment of HFpEF: why we have no evidence."

Finally, this issue's Case Report article by Jessica Webb summarizes a patient with a constellation of symptoms, signs, and imaging findings that were consistent with HFpEF. To finalize the diagnosis, the patient underwent right and left heart catheterization, including pressure-volume analysis of the left ventricle. The case report illustrates the ability of invasive studies to characterize key parameters of diastolic compliance and clarify the diagnosis. It also reminds us that elevated left ventricular filling pressure is the hallmark of HFpEF. Unfortunately, there is only one way to directly measure pressure, but invasive studies are not appropriate in the majority of patients with HFpEF due to their age and comorbidities. In addition, making the diagnosis will not dramatically alter therapy.

I found editing this issue both stimulating and depressing! It brought home to me that we still understand little about the complex and heterogeneous conditions that lead to the HFpEF syndrome. At the moment, all we can do is identify and treat its predisposing risk factors and hope that ultimately there will be a specific therapy that suggests it is more than just a sum of these parts. ■