JACC: HEART FAILURE VOL. 6, NO. 8, 2018

PUBLISHED BY ELSEVIER

EDITOR'S PAGE

HFpEF

From Early Observations to Worldwide Awareness

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We have dedicated the August issue of *JACC: Heart Failure* to the condition of HFpEF—heart failure with preserved ejection fraction. I recall as a house officer in the mid-1980s taking care of patients on the cardiology service with HF and concomitant pulmonary edema. In our initial evaluations, we were often surprised to see that these patients had normal ejection fractions; they were often elderly women with multiple comorbidities. Our work-up would include ruling out myocardial ischemia and arrhythmias, and we were left searching through the medical records to see whether there were significant elevations in blood pressure that may have explained the presentation.

The earliest description of HFpEF was by Robert Luchi in 1982 (1). Dr. Luchi noted that in his patients >75 years of age admitted with acute congestive HF, nuclear imaging studies, a relatively new development at the time, frequently showed a relatively normal left ventricular ejection fraction (LVEF), rather than the severely reduced LVEF that was universally thought to be a requisite for HF (1).

During my time as a house officer, Eric Topol (2) published in the *New England Journal of Medicine* a series of 21 elderly hypertensive female patients with severe concentric cardiac hypertrophy, normal ejection fraction, and HF symptoms. This characterization of the suspected new clinical condition more than 33 years ago led to significant increase in investigations of the condition that was barely understood as a clinical entity at the time. Early studies focused on careful measurements of diastolic dysfunction, and the condition was defined by these parameters. Later, it was noticed that up to 30% of patients who presented with clear signs and symptoms of HF with a normal ejection fraction did not present evidence of diastolic dysfunction as determined by careful echocardiographic measurements. Thus, the clinical condition evolved in its characterization from diastolic dysfunction HF to HF with normal ejection fraction to HF with preserved ejection fraction.

Subsequently, as we have continued to refine the ejection fraction cutoff from 40% to 50%, we have now entertained an intermediate condition known as HF with midrange ejection fraction that is between 40% and 50% (3). There is a convergence of investigations that occurred from many laboratories across the world looking at mechanisms of exercise intolerance with invasive hemodynamic exercise studies, metabolic gas exchange, and using cardiopulmonary exercise and biological markers to gain a better understanding of the pathophysiological mechanism of these patients.

In parallel, large registries such as the ADHERE (Acute Decompensated Heart Failure National Registry) and OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) registries began to characterize this population and recognized that 50% of the patients admitted to hospitals with HF indeed had normal ejection fractions (4,5). These patients also had a significant rate of morbidity and mortality following discharge, including similar rates of rehospitalization over the next 90 days as patients with HF and reduced ejection fraction. It was also noted that a significant number of patients with HF and preserved ejection fractions had evidence of pulmonary hypertension. In addition, comorbidities such as obesity, hypertension, diabetes, atrial fibrillation, and ischemic heart disease were common in these patients. Because of the understanding that the renin-angiotensin system (RAAS) is activated in hypertensive patients and that drugs targeted toward the RAAS system had been successful in the treatment of hypertension, a number of clinical trials were initiated and completed looking at RAAS inhibition in patients with HF with preserved ejection fraction.

ISSN 2213-1779/$36.00 https://doi.org/10.1016/j.jchf.2018.07.001

Unfortunately, the series of these trials did not result in the signals that we had seen in patients with HF with reduced ejection fraction. This led many investigators to change their direction of investigation to consider other potential mechanisms for the underlying pathophysiology, including myocardial fibrosis, endothelial dysfunction, and inflammation. Continued research and investigation occurred in parallel with beta-blocker therapy in this population and did not result in direct benefit. The randomized controlled trial of spironolactone targeting potential mechanisms of myocardial fibrosis did not reach its primary endpoint (6). A clinically relevant signal was found in North American patients, leading to additional trials of aldosterone antagonism to determine whether trial characteristics versus drug therapy signals were behind the failure to achieve a positive primary endpoint.

Today, as you can see in this issue committed to HFpEF, there are many important concepts of future strategies that will guide potential therapies for the patients we serve. It is clear that inflammation and comorbidities play a major role in the increased morbidity and mortality of these patients. Control of hypertension with multiagent therapies and control of diabetes with the new SGLT2 inhibitors appear to have potential signals of benefit in patients with these comorbidities and preserved ejection fraction. The PARAGON-HF (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction) trial of sacubitril/valsartan supports much excitement about the potential for this strategy. Integrating with not only the RAAS system, but also endothelial function and renal function among other mechanisms. Attempts to target secondary pulmonary hypertension and endothelial function with nitrates have proven not to be beneficial. Device therapies targeting elevated left atrial pressures creating intracardiac shunts may also hold promise for the future. Further analysis of large datasets suggest that it is naive to think that the phenotype of HFpEF is a uniform one. Phenomapping strategies to characterize this patient population into 3 or 4 categories offers the best chance for future therapeutic interventions.

In summary, over the lifetime of my career from house officer to senior investigator, the community of HF clinicians have worked together to improve our understanding, treatment, and overall, worldwide awareness of this condition that began as an early observation by astute clinicians and has continued to keep the momentum by tackling the morbidity and mortality while improving quality of life associated with HFpEF.

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