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Guest Editorial

Hypertension and Heart Failure with Preserved Ejection Fraction

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In the past four decades, there is an increase in the incidence and prevalence of heart failure. It is the most common cause of hospital admission after the age of 65-year-old individuals. In heart failure, there is structural and functional impairment of ventricular filling or ejection of blood. More than 75% of heart failure patients have antecedent hypertension. Hypertension accounts for 39% of risk in men and 59% of risk in women. Elevation of blood pressure leads to structural changes in the myocardium which, in turn, results in heart failure. Based on ejection fraction, the heart failure is classified as heart failure with reduced ejection fraction (HFrEF) when the ejection is <40%, and when the ejection fraction is >50%, it is known as heart failure with preserved ejection fraction (HFpEF). Nearly half of all the patients with heart failure have HFpEF. HFpEF continues to increase in prevalence due to common risk factors such as hypertension, old age, female sex, metabolic syndrome, and obesity. Hypertension, in particular, is a strong risk factor, and 80–90% of the people with hypertension have HFpEF. Historically, HFpEF was termed as diastolic heart failure, and this terminology is no more used now because recent investigations suggest a more complex and heterogeneous pathophysiology for HFpEF apart from diastolic dysfunction.

Heart failure	Ejection fraction
HFrEF	<40%
HFpEF	>50%
Heart failure with borderline or midrange EF (HFmrEF)	40–49%
HF-recovered EF	EF improved from HFrEF to >40%

HFpEF is prevalent but incompletely understood syndrome. Alterations in passive ventricular stiffness, ventriculoarterial coupling, and microvascular function occur. HFpEF is a heterogeneous state in nature and it is difficult to prescribe uniform therapies to all patients. Treating hypertension is the cornerstone of HFpEF. Antihypertensive therapies have been linked to LV hypertrophy regression and improvement in diastolic dysfunction. However, to date, no therapy has definitive mortality benefit in HFpEF. Non-pharmacological management for hypertension, including dietary modification and exercise, may provide some morbidity benefit in the HFpEF population. When compared to patients with HFrEF, patients with HFpEF are older and less likely to have ischemic etiology. The mortality in HFrEF is reduced as a result of a number of evidence-based medical therapies, but in contrast in HFpEF, the mortality outcomes have not improved.

Hypertension remains as one of the major modifiable risk factors in HFpEF development and progression. The model of HFpEF pathophysiology emphasizes the role of hypertension causing LV hypertrophy and LV diastolic dysfunction. In the hypertrophied myocardium, there are limited vasodilation and altered electrical properties that can change the global function of the heart. Diastolic dysfunction is defined as the inability of LV to expand and relax, and it can be determined by echocardiographic studies. HFpEF is a heterogeneous disease entity with multiple contributors to its pathophysiology. A new paradigm for HFpEF was recently proposed where comorbid conditions including hypertension, diabetes, and obesity promote a pro-inflammatory state that leads to the development of HFpEF. It is postulated that systemic pro-inflammatory state leads to the development of coronary microvascular endothelial dysfunction, with subsequent reductions of nitric oxide bioavailability. Correction of protein kinase G activity and increasing nitric oxide bioavailability have been suggested for the treatment of HFpEF.

Prevalence of HFpEF is common in hypertensive individuals and elderly population. Atrial fibrillation is the common arrhythmia seen patients having HFpEF. The incidence of coronary artery disease is lower in patients with HFpEF. The other causes of abnormal diastolic function are hypertrophic and restrictive cardiomyopathies, coronary artery disease, diabetes mellitus, obesity, sleep apnea, chronic kidney disease, and aortic stenosis. LV filling may be impaired by abnormal active relaxation (early filling phase) and passive ventricular stiffness (late filling phase). HFrEF involves progressive expansion of the ventricle (LV dilation) and elongation of myocytes. HFpEF triggers a hypertrophic response with a marked increase in fibrosis leading to

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concentric remodeling without LV dilation. In HFpEF, ventricular hypertrophy, role of neurohormones, inflammatory process, and impaired cardiac relaxation are involved. HFpEF can progress to HFrEF, and diastolic dysfunction can occur in HFrEF.

Diagnosis of HFpEF is based on three factors: (1) Signs and symptoms of heart failure, (2) echocardiographic abnormalities such as increased LV mass and LA size and presence of Doppler parameters of diastolic dysfunction, and (3) elevated levels of brain natriuretic peptides (BNP). BNP levels are increased in HFrEF also.

Parameter	Clinical presentation (%)	
	HFpEF	HFrEF
Dyspnea	60	73
Paroxysmal nocturnal dyspnea	55	50
Pedal edema	35	46
Lung crepitations	72	70
Fatigue	+	+
Loss of appetite	+	+
Elevated JVP	+	+

1. Doppler interrogation of transmitral valve flow with E and A velocity ratio.
2. Pulmonary venous flow pattern.
3. Tissue Doppler assessment of E/E' ratio
4. Color flow M-mode measurements.

All these four assessments are very useful to assess the grading of LV diastolic dysfunction. Echocardiography in HFpEF will show the features of diastolic dysfunction, LA enlargement, LV hypertrophy, LA volume index >34 mL/m^2, and increased LV mass index.

Management of HFpEF is started with lifestyle modification such as reduction of salt intake, control of body weight, and regular physical exercise.

Therapeutic strategies are as follows:

1. Control of hypertension
2. Control of pulmonary congestion and peripheral edema with diuretics
3. Control of heart rate in atrial fibrillation
4. Coronary revascularization in patients with CAD.

The common drugs used in HFpEF are diuretics, verapamil, digoxin, beta-blockers, nitrates, ACE inhibitors/ARBs, aldosterone antagonists, and statins.

The treatment targets and options include,

LV volume and edema - diuretics, salt restriction

Hypertension - diuretics, CCBs, BB, ACEIs, ARBs

Reverse LVH - most antihypertensives

Prevent ischemia - BB, nitrates, CCB

Reduce heart rate in AF - BB, CCB, digoxin

Prognosis of HFpEF is as bad as HFrEF. Studies utilizing a variety of agents such as beta-blockers, calcium channel blockers, and diuretics demonstrated regression of LV hypertrophy, though the renin-angiotensin aldosterone blockers lead to higher rates of LVH regression. In perindopril in elderly people with chronic heart failure trial, there was a trend toward a reduced mortality and heart failure hospitalization with perindopril therapy. Candesartan in heart failure reduction in mortality trial assessed the role of candesartan, and there was a significant reduction in hospitalizations. Irbesartan in patients with heart failure and preserved ejection fraction (I-PRESERVE) trial, there was no significant difference in primary endpoint of all-cause mortality or hospitalizations. The valsartan in diastolic dysfunction trial demonstrated reductions in blood pressure and improvements in diastolic dysfunction. Recently, angiotensin receptor neprilysin inhibitors have generated much interest. To date, Valsartan-Sacubitril therapy outcome is encouraging in reducing the left atrial size and systolic blood pressure.

In the treatment of preserved cardiac function heart failure with aldosterone antagonist trial, the frequency of hospitalizations was less with spironolactone therapy, LA size reduction is noticed, decrease in pulmonary venous flow reversal occurs, and significant improvement is noted in diastolic dysfunction in echocardiographic assessment. A study of the effects of Nebivolol Intervention on outcome and rehabilitation in seniors with heart failure trial compared nebivolol with placebo in elderly patients. There was a reduction in all-cause mortality and hospitalizations. ALLHAT trial demonstrated a reduction in new-onset hospitalization incidence with chlorthalidone. Dig trial with digoxin reduces the ventricular rate in atrial fibrillation.

Conclusion

The overall prognosis of HFpEF is bad as HFrEF. Hypertension frequently contributes to the pathophysiology of HFpEF. HFpEF is recognized as a multifactorial syndrome. Management of hypertension is the cornerstone of HFpEF management, and careful matching of antihypertensive treatment holds a great promise for improving outcomes in patients with HFpEF.

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