Heart Failure with Preserved Ejection Fraction in the Elderly: Challenges and Management

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Key Points

- In elderly, heart failure with preserved ejection fraction (HFPEF) is a prominent cause of hospitalization.
- The syndrome often coexists with other common morbidities.
- This condition is caused by abnormalities affecting left ventricular relaxation.
- Control of symptoms and risk factors and treatment of comorbid conditions are the important steps in management.
- The long-term prognosis is similar to that of heart failure with reduced ejection fraction.

Case Study

Mr. AB, an 83-year-old obese gentleman, presents with worsening shortness of breath and fatigue over the past 2 weeks. He also noticed increasing bilateral ankle swelling and weight gain in the same duration. While trying to get up from bed, he feels dizzy and light headed. He is known to have hypertension for the last three 3 decades for which he is on lisinopril 20 mg and chlorthalidone 12.5 mg and has diabetes for which he has been advised long-acting insulin as well as oral medications. Apart from these, he is on tamsulosin for symptomatic prostatic hypertrophy. Fifteen years ago, he had pacemaker implanted for symptomatic sick sinus syndrome with sinus bradycardia and had the pulse generator replaced 4 years ago. There is a history of inferior wall myocardial infarction 10 years ago for which he underwent primary angioplasty with drug-eluting

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coronary stent implantation and is on 81 mg ASA and nitrates and 20 mg of rosuvastatin daily. His wife reported gradual decline in his activities, listlessness, and increased daytime somnolence before the recent deterioration. She also is not sure about the adherence to bedtime medications since she retires before him.

In the ER, he is tachypneic, and saturations are 90% at room air. His pulse rate is 60 beats per minute, regular, and blood pressure is 180/75 mmHg. Jugular veins are visible at 12 cm with absent a wave, prominent v wave, and y descent. Cardiovascular system examination reveals cardiac enlargement, soft first heart sound, single and loud second heart sound, and an early peaking ejection murmur of mild aortic stenosis. There are fine rales over the lung bases suggestive of heart failure. There is pitting edema of both legs.

His ECG reveals absent P waves and a regular broad QRS paced rhythm at 60/min. Biochemistry shows normal troponins, NT-Pro BNP value of 8000 pg/mL, serum sodium 135 mmol/L, potassium 3.6 mmol/L, creatinine of 1.5 mg/dL with a calculated GFR of 48, hemoglobin of 6.5 g%, normal total and differential leucocyte counts, serum total protein of 7 g/dL, albumin of 3.4 g/dL, and normal bilirubin and liver enzymes and TSH. Stool guaiac test turns out to be positive. HbA1c level is 6.8%.

An echocardiogram demonstrated left ventricular hypertrophy, mild dilatation of the ventricles, global left ventricular function of 52%, dilated atria, and sclerosed aortic valve with mild transvalvular gradient. There is mild mitral regurgitation also. The estimated pulmonary artery systolic pressure is 60 mmHg.

Review of his previous medical records reveals that he had undergone last pacemaker check 9 months ago and was noted to have predominantly paced ventricular beats with occasional atrial pacing.

How should we manage Mr. AB and optimize his medical treatment?

17.1 Introduction and Definition

Almost half of the patients with congestive heart failure in various registries were detected to have normal left ventricular ejection fraction [1]. This entity found its expression in the term diastolic heart failure [2] and subsequently with a wider scope as heart failure with preserved ejection fraction, when it was found that this entity has distinct epidemiological and pathophysiological features and therapeutic challenges. Currently, the diagnosis is invoked when a patient presenting with typical symptoms, signs, and biochemical evidence of heart failure has features of left ventricular diastolic dysfunction in imaging or cardiac catheterization and an ejection fraction of 50% or higher while noncardiac causes of symptoms of HF are excluded (Table 17.1).

17.2 Epidemiology

The prevalence of HFPEF increases with age, and the incidence doubles every decade after the age of 65 years. HFPEF is the leading cause of hospitalization in this age group [7]. Almost one in ten of those aged ≥ 80 years has this condition [8]. The

Table 17.1 Definitions of HFPEF used in various guidelines—a synopsis

ESC 2012 [3]	HFSA 2010 [4]	ACC/AHA 2013 [5]	ESC 2016 [6]
Symptoms and signs typical of HF BNP > 100 pg/mL NT-proBNP > 800 pg/mL	Clinical signs/ symptoms of HF Lab: biomarkers or chest X-ray or cardiopulmonary exercise testing	HFPEF: EF ≥ 50%, diastolic HF. Exclude other potential noncardiac causes of symptoms suggestive of HF	Symptoms/signs of HF LVEF ≥ 50% Elevated natriuretic peptides[a] • *Acute setting*: – BNP ≥ 100 pg/mL – NT-proBNP ≥ 300 pg/mL • *Non-acute setting*: – BNP > 35 pg/mL – NT-proBNP > 125 pg/mL
Normal or only mildly decreased LVEF and LV not dilated (LVEDV ≤ 97 mL/m^2 or indexed LVEDV ≤ 49 mL/m^2)	Preserved LVEF > 50% Normal LVEDV	HFPEF borderline: EF 41–49%. Characteristics, treatment patterns, and outcomes are similar to those of patients with HFPEF	
Relevant structural heart disease (LV hypertrophy or left atrial enlargement) and/or diastolic dysfunction in echocardiography or cardiac catheterization	Use echocardiography, ECG, stress imaging, or cardiac catheterization to distinguish HFPEF and other disorders Exclude non-myocardial disease	HFPEF improved: EF > 40%. Includes a subset of patients with HFPEF who previously had HFREF	At least one additional criterion: (a) Relevant structural heart disease (LVH and/or LAE) (b) Diastolic dysfunction

ESC European Society of Cardiology, *HFSA* Heart Failure Society of America, *ACC* American College of Cardiology/*AHA* American Heart Association. *HF* Heart failure, *BNP* B natriuretic peptide, *LV* left ventricle, *LA* left atrium, *EDV* end diastolic volume, *LVH* LV hypertrophy, *LAE* LA enlargement (adapted from [3, 4, 5, 6])

[a]The values of natriuretic peptides according to the ESC 2016 guidelines are more useful to exclude a diagnosis of HF in the appropriate setting; the positive predictive value of elevated concentrations is lower

5-year survival of patients with HFPEF is almost similar to those with HFREF (heart failure with reduced ejection fraction) and is approximately 50% [9]. Patients with HFPEF are more likely to be elderly women, hypertensive, and diabetic and have atrial fibrillation. More than a fourth (30%) of the patients with HFPEF die of non-cardiovascular causes, while sudden cardiac death accounts for another fourth [10]. As age advances, the prevalence of comorbidities like sleep apnea, chronic kidney disease, and COPD increases as do the prevalence of cardiovascular diseases and risk factors. All these contribute significantly to the development of HFPEF in this age group.

In addition, HF is one of the commonest comorbidity in hospitalized elderly patients, with poor outcomes and prolonged hospital stay.

17.3 Aging and Heart Failure

The process of aging affects the myocardium, vasculature, and results in the activation of the neurohumoral system. Consequent to the increase in collagen and decrease in elastin, the vessels become stiffer, which is compounded by calcification. This increases the afterload and has effects on cardiomyocytes with hypertrophy, fibrosis, and alterations in calcium intake in sarcoplasmic reticulum, resulting in decreased diastolic reserve. The rate of early diastolic filling of the left ventricle decreases in the elderly [11]. The mitochondria in the cardiac myocytes of the elderly have decreased capacity to generate ATP adequately during stress, thereby limiting the peak myocardial performance. The vasodilatory reserve of the vasculature is affected by reduction in the synthesis of endothelial nitric oxide and atherosclerotic changes. Neurohumoral blunting manifests as chronotropic incompetence, decreased heart rate variability, and decreased augmentation of cardiac output in response to exercise. Comorbidities like hypertension, diabetes, renal dysfunction, and obesity result in exacerbation of stiffening of ventricles and arteries. All these result in marked decline in cardiovascular reserve, and elderly are often unable to maintain a normal cardiac output in response to physiological stress like exercise or pathological processes like anemia, infection, myocardial ischemia, etc. (Table 17.2).

Table 17.2 Common conditions which predispose to HF in the elderly

Hypertension
Myocardial ischemia
Excess salt intake
Arrhythmias, especially atrial fibrillation
Anemia
Infections/sepsis
Renal dysfunction
Alcohol
Lung disease
Thyroid dysfunction
Obstructive sleep apnea

17.4 Hemodynamics of Diastolic Dysfunction

Decreased left ventricular compliance affects the LV filling, characterized by disproportionate increase in LV diastolic pressure in response to rise in LV volume. This causes left atrial hypertension and results in pulmonary venous congestion, pulmonary hypertension, and, subsequently, systemic venous congestion. Impaired LV filling also manifests as lower forward cardiac output, even when the ejection fraction is not affected significantly. Ventricular relaxation abnormalities cause left atrial hypertrophy predisposing to atrial fibrillation, which in turn contributes to loss of forward cardiac output. In patients with advanced diastolic dysfunction, atrial systole contributes to 25–30% of stroke volume, and when they develop atrial fibrillation, the loss of this "booster pump effect" renders them more symptomatic.

17.5 HFPEF in the Elderly: Clinical Challenges

17.5.1 Diagnosis

The symptoms of HFPEF in the elderly could overlap with that of general frailty. The elderly often present with fatigue that could be attributed to aging and other comorbidities, and HF in such patients might go on undiagnosed. Atypical symptoms like confusion, anorexia, and decreased levels of physical activity could be the presenting symptoms in the very elderly. Eliciting a history could be challenging with cognitive impairment. Physical findings are often not as helpful as in younger patients. Signs such as ankle edema could occur due to chronic venous insufficiency or from calcium channel blockers. Crackles over lung fields could be due to chronic lung disease or atelectasis.

Echocardiographic evaluation is useful to diagnose this condition, especially velocities of mitral valve flow and mitral annular tissue Doppler imaging. Aging itself is associated with features of mild diastolic dysfunction like prolongation of isovolumic relaxation time, decrease in early mitral inflow velocity, and prolongation of early ventricular filling time in Doppler. Findings of advanced diastolic dysfunction are obtained during echocardiography in severe cases. The various stages of ventricular diastolic dysfunction and the echocardiographic features are listed in Table 17.3; excellent reviews are available which provide detailed discussion on echocardiographic features of diastolic dysfunction.

Biomarkers such as brain natriuretic peptide (BNP) and N-terminal ProBNP are useful to improve the diagnostic accuracy in elderly with dyspnea and nonspecific symptoms. However, the cutoff values for BNP and NT-proBNP for patients older than 75 years are almost two- and fourfold higher, respectively, than those for patients younger than 75 years. Likewise, the cutoff is higher for women and patients with renal dysfunction. In the PRIDE study [12], the sensitivity and specificity of plasma levels of NT-ProBNP >1200 pg/mL for patients with GFR <60 mL/min/1.73 m^2 was 89% and 72%, respectively, as against 85% and 88% for the following cutoffs in patients with GFR ≥ 60 mL/min/m^2 (>450 pg/mL in those less

Table 17.3 Echocardiographic features of various grades of diastolic dysfunction

Parameter	Grade 0	Grade I	Grade 2	Grade 3a	Grade 3b
Nomenclature	Normal	Abnormal Relaxation	Pseudonormalized	Reversible restrictive dysfunction	Irreversible restrictive dysfunction
Hemodynamic abnormalities		– ↑ early LV diastolic pressure – LA pressure normal at rest – ↓ and slow early LV filling, compensated by late filling	– LA pressure increases restoring the early filling – LV relaxes slowly after entry of blood in LV inflow from LA – Early diastolic LV filling gets completed quickly due to the shift in pressure-volume relationship	– Further increases in LA pressure and more prominent "atrial kick" – Marked slowing and delay in LV relaxation throughout the diastole – More rapid rise in LV early diastolic pressures – Can be partly reversed by preload reduction	– The same as in 3a, but the features cannot be reversed by preload reduction (nitroglycerin, Valsalva strain)
Mitral valve Doppler	E/A 0.8–1.5 DT 140–240 ms	$E/A < 0.8$ EDT > 200 ms	E/A 0.8–1.5 EDT 160–200 ms	$E/A \geq 2$ EDT < 160 ms	
Tissue Doppler	Septal $e' \geq 8$ cm/s	Septal $e' < 8$ cm/s Average $E/e' \leq 8$	Septal $e' < 8$ cm/s, Average $E/e' = 9–12$	Average $E/e' \geq 13$	
Pulmonary vein Doppler	Ar velocity < 35 cm/s	$S/D > 1$ Ar − A duration = 0 ms	$S/D < 1$ Ar velocity ≥ 30 cm/s Ar − A duration ≥ 30 ms	$S/D < 1$ Ar velocity ≥ 30 cm/s Ar − A duration ≥ 30 ms	
Valsalva strain	E/A not changed	$\Delta E/A < 0.5$	$\Delta E/A \geq 0.5$	$\Delta E/A \geq 0.5$	E/A does not change
IVRT		≥100 ms	<60 ms	≤60 ms	

LV left ventricle, *LA* left atrium
E early LV filling wave velocity, *A* late LV filling wave velocity obtained by Doppler echocardiography
e' = mitral annular velocity during early diastole obtained using tissue Doppler imaging
E/e' = ratio of *E* and e' velocities
Pulmonary vein Doppler velocities: *S* systolic filling wave, *D* diastolic filling wave, Ar atrial reversal wave. Ar − *A* duration: difference in durations of Ar wave and late diastolic left ventricular filling wave
IVRT isovolumic relaxation time (duration between the closure of aortic valve and opening of mitral valve during diastole, when the LV volume remains unchanged, unless the patient has regurgitant valves or ventricular septal defect, in which this condition is not satisfied)

than 50 years and >900 pg/mL in older patients) to diagnose HF in 599 patients presenting to emergency with a complaint of dyspnea and having serum creatinine ≤ 2.5 mg/dL. Plasma levels of BNP and NT ProBNP are lesser in obese patients. Low plasma values of BNP (<100 pg/mL) or NT-ProBNP (<300 pg/mL) [13] in patients presenting with dyspnea have an excellent negative predictive value to exclude a diagnosis of HF. Certain other conditions could also result in higher levels of natriuretic peptides like sepsis and anemia, but usually indicative of cardiovascular impairment. Interestingly, treatment with neprilysin inhibitors (sacubitril) can increase the plasma levels of BNP, since BNP (not NT-ProBNP) is a substrate for the enzyme.

17.5.2 Comorbidities and Frailty

Elderly patients with HF often have comorbid issues which affect the management and prognosis of HF. The development of HF itself can affect such illnesses unfavorably. Some commonly associated problems and interactions are listed in Table 17.4.

Table 17.4 Comorbid conditions in elderly and their interactions

Comorbid condition	Cause	Effect
Anemia	Nutritional, chronic illnesses GI blood loss	Worsens symptoms of HF Affects prognosis Poor exercise capacity Worsens ischemia
Renal dysfunction	Ageing related Medication induced—RAAS blockers, diuretics	HF and CKD mutually impair the treatment of either Diuretics less effective in renal dysfunction Increased risk of electrolyte imbalance
Lung disease		Confounds diagnosis Worsens severity of HF with increased work of breathing
Obstructive sleep apnea		↑ sympathetic nervous system activity, ↑ LV afterload, and hypoxic pulmonary vasoconstriction, all result in reduced cardiac output Increases HF admission and mortality
Postural hypotension	Autonomic dysfunction Worsened by medications (vasodilators, diuretics)	Interferes with therapy Risk of falls Interferes with activity
Cognitive dysfunction		Interferes with medication adherence and non-pharmacological therapy
Osteoarthritis		Therapy with NSAIDs worsen HF and renal dysfunction
Stress incontinence	Common in very elderly, more in women Exacerbated by diuretics or ACE inhibitor-induced cough	Patients might skip medications without divulging this to avoid embarrassment

17.6 Management

Unlike in patients with HFREF, medications have not been shown to improve survival in patients with HFPEF. Treatment is aimed at relieving pulmonary or systemic venous congestion and management of underlying cardiac disease and the precipitating factors. These can be attempted using medications as well as with non-pharmacological approaches. While blockers of renin-angiotensin-aldosterone axis and certain beta adrenoceptor antagonists (carvedilol, metoprolol succinate, and bisoprolol) prolong survival in patients with HFREF, such therapies (angiotensin-converting enzyme inhibitors, angiotensin II receptor blocker and beta blockers) have at the best been found to improve HF admissions in some of the trials (candesartan in CHARM-Preserved trial, perindopril in PEP-CHF, and nebivolol in SENIORS showed some effect in decreasing hospitalizations with HF with the respective agents, and spironolactone did not have any effect in HFPEF in the TOPCAT trial) without any substantial effects on survival. Diuretics provide symptomatic relief though patients can develop electrolyte disturbances and have worsening of fatigue due to decrease in cardiac output.

Control of hypertension commensurate with the guidelines is the most important measure in patients with HFPEF to decrease cardiovascular events, mortality, and hospitalization for HF. Coronary revascularization could be considered in patients with significant angina or myocardial ischemia contributing to HF in patients with significant stenosis in coronary arteries. In patients with atrial fibrillation, attempts at control of heart rate or conversion to sinus rhythm might help in mitigating symptoms due to HF. Digoxin could be useful in patients with fast ventricular rate, to control the response.

The clinical evaluation of an elderly HF patient should also be aimed at identification and treatment of factor(s) which resulted in development of heart failure. Occasionally when the health care provider focuses on control of HF, the precipitating factors are overlooked. A carefully elicited history and detailed general and systemic examination might help identify situations which might be unrecognized otherwise. Elderly maintain a delicate balance which can easily be tilted by factors like altered bowel habits, sleep, infections, etc. Management should include correction of these abnormalities too.

17.7 Non-pharmacological Interventions

While observational studies have indicated increased risk of hospitalization and fluid retention in patients due to higher dietary sodium intake, other studies have indicated worse outcomes with sodium restriction in patients with HF, especially in those with HFREF. Guidelines currently recommend restricted dietary intake of sodium in patients with HF. The degree of fluid and salt restriction during acute hospitalization is decided based on the urine output and hydration status. In patients with decompensated heart failure, the lack of sodium restriction and administration of nonsteroidal anti-inflammatory drugs can result in loop diuretic resistance and worsening of HF. It is often noticed that patients develop decompensation of their heart failure status when they go easy on salt and fluid restriction or skip their medicines. Tobacco control

strategies and modification of alcohol consumption patterns should be advised when needed. Diet advice should incorporate energy requirements, since the basal metabolic rate increases by a fourth in such patients and malnutrition is common. The volume status and electrolyte balance of the patient need to be taken into consideration during planning of diet. Exercise training has been found to be effective in improving the cardiorespiratory fitness of patients with HFPEF without affecting the systolic and diastolic function significantly [14]. This could be instituted once the decompensated state improves during hospitalization and improved upon after discharge.

Management of the Patient: Continued

Mr. AB who was apparently maintaining a compensated hemodynamic profile has presented with decompensation, the precipitants of which could be evidenced from history and investigations. Anemia due to GI blood loss, possibly related to ASA, possible noncompliance with night dose of Lisinopril, obstructive sleep apnea, and recent development of atrial fibrillation seems to have resulted in his present clinical state. In addition, his wife also revealed that he occasionally took over-the-counter analgesics for osteoarthritis. A blood gas revealed hypercarbia too, and the initial management involved positive pressure ventilation. Nitroglycerin infusion could help to decrease the pulmonary venous congestion. Intravenous loop diuretics along with potassium sparing diuretic (eplerenone/spironolactone) or oral potassium supplementation with cautious monitoring of electrolytes and renal function could be instituted. Potassium sparing diuretics do not accord any survival benefit in patients with HFPEF, but in such situations might help to optimize the loop diuretic dose in the background of hypokalemia. However, the decision to continue with these groups of diuretics should be with caution, in the presence of reduced GFR. The patient's cardiac conduction abnormality has apparently worsened or has been affected by the metabolic abnormalities as suggested by the regular paced rate of 60/min. Patients with HFPEF rely significantly on the atrial booster pump action and become severely symptomatic with the onset of atrial fibrillation. The pacemaker could be programmed to faster rates so as to improve the cardiac output. Attempts at restoring atrioventricular synchrony might also be made if the patient's clinical status does not improve, and restoration of sinus rhythm might help in presence of the implanted dual-chamber pacemaker. Packed cell transfusion and optimizing antihypertensive regimen by adding on another class of medicines—beta blockers (which are acceptable since there is an implanted pacemaker)—are important considerations at this stage. Prophylaxis against venous thromboembolism might be initially restricted to non-pharmacological methods like elastic compression stockings till the evaluation of GI blood loss is complete. Monitoring weight daily adds important information to volume status of the patient. Sleep studies should be undertaken at discharge, and domiciliary positive pressure ventilation strategies may be planned. Counseling about diet, adjusting the timing of medicines, information about monitoring weight, avoidance of unsupervised nonsteroidal anti-inflammatory agents, planning the anticoagulation strategies after assessing the bleeding risk, close monitoring of renal function, and preventive strategies for postural falls should be incorporated.

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