Aldosterone Receptor Blockade in Heart Failure with Preserved Ejection Fraction

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KEYWORDS

• Aldosterone blocker • Spironolactone • Eplerenone • Heart failure with preserved ejection fraction • Heart failure

KEY POINTS

- Heart failure with preserved ejection fraction (HFpEF) is a complex disorder with variable clinical phenotypes.
- Clinical trials in HFpEF have failed to show an effective therapy that has provided mortality benefit.
- Aldosterone is key mediator of myocardial fibrosis and has shown efficacy in reducing collagen turnover and in potentially improving structure and diastolic function in HFpEF.
- Although the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial failed to show a reduction in its primary end point, there was a reduction in heart failure hospitalizations for patients with HFpEF. Regional differences may have accounted for the negative results.
- Use of aldosterone antagonists may be appropriate for carefully selected patients with HFpEF who have clinical heart failure, increased brain natriuretic peptide levels, and lower risk for renal dysfunction or hyperkalemia.

INTRODUCTION

Heart failure (HF) is a leading cause of morbidity and mortality throughout the world. An estimated 6.5 million Americans greater than or equal to 20 years of age have clinical HF.[1,2] About 50% of patients with clinical HF have HF with preserved ejection fraction (HFpEF), which carries a mortality comparable with that of patients with reduced ejection fractions and is associated with significant morbidity caused by frequent hospitalizations as well as impaired functional capacity.[3,4] Patients with HFpEF tend to be elderly, female, and obese, and have comorbidities including hypertension, coronary artery disease, atrial fibrillation, and diabetes, which can contribute significantly to complications and mortality.[5,6] HFpEF represents a heterogeneous disorder with a complex pathophysiologic basis. Clinical trials to date have failed to show a therapy that definitively imparts a mortality benefit in HFpEF. Because of its effects on myocardial fibrosis and vascular function, use of mineralocorticoid receptor antagonists (MRAs) has been of particular interest in HFpEF. This article explores the basis for using aldosterone receptor antagonists in HFpEF and the current knowledge about their effects in patients with HFpEF.

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PATHOPHYSIOLOGIC BASIS OF HEART FAILURE WITH PRESERVED EJECTION FRACTION

HFpEF is now defined in the American Heart Association (AHA)/American College of Cardiology (ACC) HF guidelines as clinical symptoms and signs of HF with a left ventricular ejection fraction (LVEF) greater than or equal to 50%,[2] although several clinical trials have used an LVEF of greater than or equal to 45%, and a few trials have used LVEF greater than or equal to 50%. HFpEF may also be characterized by diastolic dysfunction on echocardiography, although this parameter is not present in all patients. Exercise intolerance is a key manifestation and may result from increases in filling pressures secondary to increased ventricular stiffness.

Several insults, including hypertension, diabetes, coronary artery disease, advanced age, atrial fibrillation, and sleep apnea, contribute to the development of cardiac structural abnormalities, which include increased diameter of cardiomyocytes, ventricular hypertrophy, and increased interstitial fibrosis secondary to upregulation of collagen synthesis cross-linking.[7] Other structural and functional alterations can also lead to the HFpEF phenotype. Alterations in titin, a large sarcomeric protein that functions as a molecular spring, are common in HFpEF. Increased density of shorter, stiffer titin isoforms, and hyperphosphorylation contribute to impaired relaxation.[8,9] Reduced sarcoendoplasmic reticulum Ca^{2+}-ATPase expression and extracellular matrix expansion can cause mechanical, electrophysiologic, and structural abnormalities.[10,11] Inflammation, partially driven by comorbidities, including renal dysfunction, lung disease, and obesity, is also thought to contribute to microvascular dysfunction and pulmonary vascular remodeling.[12]

The pathologic alterations combined with the influence of comorbid conditions can produce varied structural changes. Echocardiographic assessment of patients in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial showed heterogeneous patterns of ventricular remodeling, including different patterns of left ventricular (LV) hypertrophy and various degrees of left atrial enlargement and pulmonary hypertension.[13] Diastolic function was normal in one-third of patients. Greater degrees of LV hypertrophy, pulmonary hypertension, and increased LV filling pressures, as well as impaired LV systolic function determined by absolute longitudinal strain (LS), have all been shown to be predictive of HF hospitalizations and cardiovascular death.[14,15]

THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM IN HEART FAILURE

HF and hypertension are associated with activation of the renin-angiotensin-aldosterone system (RAAS). Chronic RAAS activation leads to increases in aldosterone level, which can promote an increase in extracellular matrix collagen and endothelial dysfunction. This condition can subsequently lead to LV hypertrophy, decreased ventricular and vascular compliance, and LV systolic and diastolic dysfunction (**Fig. 1**).[16] Inhibition of RAAS can reverse this process and may improve diastolic function. Although angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) can suppress angiotensin II–mediated aldosterone release, patients can have increased aldosterone levels caused by the phenomenon of so-called aldosterone escape.[17] Despite optimal ACEI or ARB therapy, multiple studies have shown that markers of collagen turnover are increased, indicating ongoing aldosterone-mediated effects. Increased myocardial stiffness and poor compliance are among the key contributors to the disorder of HFpEF and is contributed to by aldosterone-mediated increases in myocardial collagen. MRAs, including spironolactone and eplerenone, antagonize the effect of aldosterone and can lead to a reduction in fibrosis and an improvement in LV function. In animal studies, infusion of aldosterone resulted in an increase in the cardiac extracellular matrix, and the effects of aldosterone were blocked by spironolactone.[18] There is also a correlation between aldosterone levels and LV mass in patients with diastolic dysfunction and HFpEF. Thus, aldosterone promotes interstitial fibrosis and plays a central role in HF and diastolic dysfunction.

Aldosterone is derived from the zona glomerulosa of the adrenal cortex and mediates its effects partially through mineralocorticoid receptors located in the distal collecting tube of the nephron. Secretion of aldosterone is stimulated by angiotensin II, angiotensin III, and serum potassium. Mineralocorticoid receptors stimulate expression of the 3Na+/K+ pump, which drives sodium into the interstitium and potassium into the collecting duct. The resultant osmotic gradient leads to volume retention.[19,20] Spironolactone, which is a MRA and glucocorticoid receptor antagonist, and eplerenone, a selective MRA, are the two primary aldosterone receptor blockers studied in clinical trials of HF.

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