Role of spironolactone in the treatment of heart failure with preserved ejection fraction

Constantine E. Kosmas¹, Delia Silverio², Andreas Sourlas³, Peter D. Montan², Eliscer Guzman¹

¹Department of Medicine, Montefiore Medical Center, Bronx, NY, USA; ²Cardiology Clinic, Cardiology Unlimited, PC, New York, NY, USA; ³School of Medicine, University of Crete, Heraklion, Greece

Contributions: (I) Conception and design: CE Kosmas; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Constantine E. Kosmas, MD, PhD. 168-24 Powells Cove Blvd., Beechhurst, NY 11357, USA. Email: cekosmas1@gmail.com.

Abstract: Heart failure (HF) is the leading cause of morbidity and mortality globally. Heart failure with preserved ejection fraction (HFpEF) is currently responsible for about half of the patients affected with HF and is associated with impaired functional capacity, as well as significant morbidity due to frequent hospitalizations. Unfortunately, despite its poor prognosis, the management of HFpEF is very controversial and no therapy has been so far shown to reduce mortality in HFpEF. Spironolactone antagonizes the effect of aldosterone and can lead to a reduction in fibrosis and an improvement in left ventricular (LV) function. Furthermore, spironolactone decreases extracellular matrix turnover and myocardial collagen content and improves endothelial vasomotor dysfunction, mechanisms known to influence the progression of HF. Thus, given the aforementioned beneficial actions of spironolactone, extensive research has been conducted to explore the effects of spironolactone on HFpEF. Our review aims to present and discuss the clinical and scientific data pertaining to the role of spironolactone in the treatment of patients with HFpEF.

Keywords: Spironolactone; aldosterone; renin-angiotensin-aldosterone system (RAAS); heart failure (HF); heart failure with preserved ejection fraction (HFpEF)

doi: 10.21037/atm.2018.11.16
View this article at: http://dx.doi.org/10.21037/atm.2018.11.16

Introduction

Heart failure (HF) is the leading cause of morbidity and mortality globally (1). Heart Failure with preserved Ejection Fraction (HFpEF) is currently responsible for about half of the patients affected with HF and is associated with impaired functional capacity, as well as significant morbidity due to frequent hospitalizations (2).

Aldosterone, a mineralocorticoid hormone secreted by the adrenal glands, is considered a causal factor of left ventricular hypertrophy (LVH) by promoting hypertension (HTN) (3). In addition, aldosterone has also been associated with oxidative stress, endothelial dysfunction, myocardial fibrosis and vascular inflammation (4), which are well established factors in the pathogenesis of HF regardless of ejection fraction (EF) (4,5).

Chronic activation of the renin-angiotensin-aldosterone system (RAAS) exerts an important role in the initiation and progression of HF. This chronic activation leads to an increased aldosterone level, which in turn stimulates collagen accumulation, resulting in extracellular matrix expansion and endothelial dysfunction (6-8).

Even though the angiotensin converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARB) suppress angiotensin II-mediated aldosterone release, those drugs do not uniformly suppress the RAAS, resulting in elevated aldosterone levels despite therapy, a phenomenon known as the “aldosterone escape” (9).

Mineralocorticoid antagonists (MRAs), such as spironolactone and eplerenone, have already been shown...
to reduce total and cardiovascular mortality in heart failure with reduced ejection fraction (HFpEF) when administered on top of ACE-I, ARB and beta blockers (10,11).

Spironolactone antagonizes the effect of aldosterone and can lead to a reduction in fibrosis and an improvement in left ventricular (LV) function (6). Furthermore, spironolactone decreases extracellular matrix turnover and myocardial collagen content and improves endothelial vasomotor dysfunction, mechanisms known to affect the progression of HF (12-14).

Thus, given the aforementioned beneficial actions of spironolactone, substantial research has been conducted to explore the effects of spironolactone on HFpEF. Our review aims to present and discuss the clinical and scientific data pertaining to the role of spironolactone in the treatment of patients with HFpEF.

Pathophysiology of HFpEF

HFpEF, also referred to as diastolic HF, is a clinical entity characterized by signs and symptoms of HF with a normal or low-to-normal ejection fraction. Its incidence and prevalence increase with age (7).

Conventionally, affected individuals present normal LV volume and signs of diastolic dysfunction, such as slowed LV filling and increased filling pressures secondary to increased ventricular stiffness, prolonged isovolumetric LV relaxation and increased LV end-diastolic pressure (7,15).

Several conditions contribute in the pathogenesis of HFpEF, among them advanced age, HTN, diabetes, coronary artery disease (CAD) and atrial fibrillation, resulting in the development of cardiac structural abnormalities, such as LVH, left atrial dilation and collagen accumulation, leading to extracellular matrix expansion, increased interstitial fibrosis and LV stiffness (7,16,17).

Additionally, dysregulation of titin, a large elastic protein expressed in cardiomyocytes, has been associated with increased cardiomyocyte resting tension or passive stiffness. This protein stores energy during contraction and releases it during relaxation. Changes in the phosphorylation state of titin, or formation of disulfide bridges within the titin molecule, brought about by oxidative stress, have been detected in isolated cardiomyocytes from subjects with HFpEF (17).

Spironolactone in the management of HFpEF

An important factor in the successful management of HFpEF is the reduction or the control of the multiple comorbidities associated with this condition, such as HTN, diabetes and atrial fibrillation. In this regard, effective reduction of blood pressure levels decreases LV hypertrophy, reduces LV end-diastolic pressure and improves LV relaxation and filling, thus resulting in a reduction of the progression of HF (18).

MRAs have been of particular interest in the management of HFpEF due to their effects on interstitial fibrosis, myocardial stiffness, extracellular matrix expansion and vascular function, which are all key components in the pathogenesis of HFpEF (6,19).

Spironolactone therapy has been shown to improve the indices of diastolic dysfunction on echocardiography and to decrease procollagen type III N-terminal propeptide accumulation, a circulating marker of myocardial fibrosis (20). Furthermore, there is evidence that spironolactone prevents LV fibrosis and remodeling after myocardial infarction (21,22).

The Aldo-DHF trial was a multicenter, prospective, randomized, double-blind, placebo-controlled trial, which studied the effect of spironolactone on diastolic function and exercise capacity in 422 patients with HFpEF. The follow-up period of the trial was 12 months and the patients were randomly allocated to receive 25 mg of spironolactone once daily versus matching placebo. Therapy with spironolactone led to an improvement in diastolic function and induced reverse LV remodeling but did not influence maximal exercise capacity, patient symptoms, or quality of life in patients with HFpEF (23).

In the randomized, double blind Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, which included 3,445 patients with symptomatic HF and an EF ≥45%, the patients were randomly allocated to receive 15–45 mg of spironolactone once daily versus matching placebo with a mean follow-up period of 3.3 years. In this trial, spironolactone failed to produce a significant reduction in the incidence of the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure (24). However, there was a significant correlation between the effect of spironolactone therapy and levels of the natriuretic peptides (NP), with most of the favorable effects of spironolactone observed in subjects with low NP levels, whereas there was no demonstrable benefit in the patients with high NP levels (25).

In a meta-analysis of 14 randomized controlled clinical
trials, which included 6,428 patients with HFrEF or myocardial infarction with preserved ejection fraction, MRA therapy reduced the number of hospitalizations for HF by 17%, improved diastolic function, induced a reversal of cardiac remodeling and improved quality of life. However, MRA therapy failed to decrease all-cause mortality (26).

In another review of 7 clinical studies evaluating the effects of spironolactone therapy in patients with HFrEF, the incidence of hospitalization for heart failure was significantly lower in the spironolactone group, as compared to placebo. In addition, spironolactone improved diastolic function and caused beneficial remodeling via a reduction in myocardial fibrosis (27).

In the Spironolactone in Myocardial Dysfunction with Reduced Exercise Capacity (STRUCTURE) trial, spironolactone therapy significantly improved the exercise capacity in patients with HFrEF and abnormal diastolic response to exertion. This spironolactone-induced improvement in exercise capacity was mediated by an improvement in the ratio of early mitral inflow velocity to mitral annular early diastolic velocity (E/e’) during exercise. Thus, the authors suggested that identification of an elevated LV filling pressure induced by exercise in subjects with HFrEF may select out a subgroup of patients with a higher likelihood of a beneficial response to spironolactone therapy (28).

However, in a large meta-analysis, which included 16,321 patients from 15 randomized controlled trials, MRA therapy led to a decreased risk of cardiovascular death, all-cause mortality, and cardiac hospitalizations in subjects with HFrEF but these benefits were not demonstrated in patients with HFrEF. Furthermore, MRA therapy was associated with an increase in the risk of hyperkalemia, whereas treatment with non-selective MRAs was associated with an increase in the incidence of gynecomastia (29).

Conclusions and future directions

From the above review of the clinical and scientific data, one can conclude that although spironolactone appears to improve diastolic function, induce reverse LV remodeling, and even reduce cardiac hospitalizations and improve quality of life in some studies, on the other hand, there is no definitive demonstrable beneficial effect of spironolactone on all-cause and cardiac mortality in patients with HFrEF. Nonetheless, spironolactone remains as a therapeutic option for HFrEF in patients with evidence of exercise-induced elevation of LV filling pressure, lower NP levels, and structural evidence of diastolic dysfunction with preserved renal function.

Furthermore, as it was alluded before, spironolactone may be more beneficial in certain subgroups of patient with HFrEF. On the other hand, certain other subgroups of patients with HFrEF may be resistant to the favorable effects of spironolactone. In a very recent study, which investigated 381 patients with HFrEF from the Aldo-DHF trial, it was clearly shown that a biochemical phenotype of high collagen cross-linking selects out subjects with HFrEF who are resistant to the favorable effects of spironolactone on LV diastolic dysfunction. The authors postulated that extensive collagen cross-linking, which stabilizes collagen type I fibers, limits the capability of spironolactone to decrease collagen deposition in these patients (30).

Given the above, it becomes evident that further randomized controlled trials are required for a more definitive assessment of the effects of spironolactone in subjects with HFrEF and to potentially identify the subgroups of patients with HFrEF that are most likely to benefit from spironolactone therapy.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

6. Nair A, Deswal A. Aldosterone Receptor Blockade in
Heart Failure with Preserved Ejection Fraction. Heart Fail Clin 2018;14:525-35.


29. Berbenetz NM, Mrkobrada M. Mineralocorticoid receptor antagonists for heart failure: systematic review and meta-