Effect of Angiotensin-converting Enzyme Inhibitors in Heart Failure Treatment

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Abstract. Heart failure is a long-term, progressive disease where the heart fails to supply sufficient blood for the body. It is a major disease contributor to global morbidity and mortality, especially among the elderly. Common causes of HF include hypertension, cardiomyopathy and ischemic heart disease, all these diseases contribute to cardiac dysfunction. A central mechanism contribute to HF is the overactivation of the renin–angiotensin aldosterone system (RAAS), which leading to vasoconstriction, fluid retention, and cardiac remodeling. Angiotensin-converting enzyme inhibitors (ACEIs) is an important drug of HF treatment. By blocking the conversion of angiotensin I to angiotensin II, thereby reducing heart burden and fluid overload, lower blood pressure, and against structural damage. Clinical studies show that ACEIs relieve symptoms, slow disease progression, and reduce hospitalization and mortality rates. However, ACEIs also has side effects such as cough, hypotension and hyperkalemia. This paper analyzes the role of RAAS in HF progression and reviews how ACEIs affects blood pressure and cardiac remodeling, while it also evaluates safety concerns related to side effects and patient tolerance. The findings show both the protective benefits and limitations of ACEIs, offering a reference for future research in HF treatment.

Keywords: Angiotensin-converting enzyme inhibitors (ACEI), heart failure (HF), renin–angiotensin aldosterone system (RAAS).

1. Introduction

Heart failure (HF) is a long-term and progressive disease where the heart muscle is unable to pump blood effectively to the rest of body. It is a major cause of morbidity and mortality in the world, especially in aging populations. HF is a serious disease, estimated that around 64 million people suffer from this disease, especially among the 60 years old people [1]. The underlying causes of HF varied, including ischemic heart disease, hypertension, and cardiomyopathy [2]. which leads to structural and functional damage in the heart. A key pathological mechanism is the overactivation of the renin–angiotensin aldosterone system (RAAS) in HF, promoting adverse cardiac remodeling, vasoconstriction, and fluid retention.

Angiotensin-converting enzyme inhibitors (ACEIs) are widely used in treatment of HF, which blocks the RAAS by inhibiting the conversion of angiotensin I to angiotensin II, leading to lower blood pressure, reduced afterload, and protection against structural damage to the heart. Many clinical trials have shown that ACEIs improve survival, slow disease progression, and reduced hospitalization rates by reduced ejection fraction (HFrEF) [3]. Most existing studies on ACEIs focus on clinical outcomes such as symptom relief and blood pressure control.

The aim of this paper is to summarize their effects on cardiac structure, function, and neurohormonal regulation, especially the RAAS. By reviewing these mechanisms, the paper seeks to provide a broader understanding of ACEI actions and support future research in HF management.

This study will focus on the effects of ACEI in the treatment of HF. It will first outline the pathological mechanisms underlying HF, emphasizing the role of renin–angiotensin–aldosterone system. Second is ACEI drugs clinical application research status and finally, discuss the current research status of ACEIs in clinical application, the effectiveness of reducing morbidity and mortality will be evaluated, and their safety will be expounded from aspects such as adverse reactions, drug tolerance and benefit assessment.

2. Pathological Mechanism of HF

2.1. Causes of HF

HF is a complex and serious clinical syndrome, and it is not a single disease, it represents the final common pathway of various cardiovascular insults. While a range of cardiovascular and systemic conditions can lead to HF, certain causes are more prevalent. Ischemic heart disease, particularly myocardial infarction, is the leading cause, as necrosis of cardiac tissue impairs contractile function [4]. Chronic hypertension increases afterload, forcing the left ventricle to work harder, which can result in myocardial hypertrophy and eventual functional decline. Valvular heart diseases, such as aortic stenosis or mitral regurgitation, create excessive pressure or volume load, further burdening cardiac performance. Inherited or acquired cardiomyopathies, as well as inflammatory conditions such as myocarditis, can also lead to HF [5]. After myocardial injury, increases in preload or afterload, or inflammatory damage, trigger adaptive changes in cellular structure and neurohormonal regulation. These processes alter functional behavior within and between cells, thereby leading to gradual remodeling of ventricular [5]. Clinically, HF is characterized by exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue, reduced exercise tolerance, and signs of fluid retention, including peripheral edema and pulmonary congestion [6].

2.2. Role of RAAS System

A central pathophysiological mechanism in HF is the maladaptive activation of the RAAS. The RAAS is a key hormonal system regulating blood pressure, fluid balance, and vascular tone, essential for cardiovascular homeostasis. It is activated by low blood sodium, reduced renal perfusion, or sympathetic stimulation via β_1-adrenergic receptors, prompting juxtaglomerular cells to release renin. Renin converts angiotensinogen to angiotensin I, then converted by ACE into angiotensin II, a potent vasoconstrictor [2, 7]. Angiotensin II acts mainly through AT1R, causing vasoconstriction, aldosterone secretion, sympathetic activation, sodium–water retention, and direct stimulation of cardiomyocyte hypertrophy and fibroblast-mediated fibrosis, increasing cardiac workload and pr0omoting adverse remodeling. AT2R mediates opposing effects, promoting vasodilation, nitric oxide release, anti-inflammatory responses, and renal protection [8]. In chronic HF, persistent angiotensin II overactivity exacerbates endothelial dysfunction, impairs diastolic relaxation, and further drives ventricular remodeling, volume overload, and increased afterload, accelerating disease progression [9, 10].

3. ACEIs

ACEIs are a cornerstone in the treatment of HF. They not only relieve symptoms, but also slow disease progression. By inhibiting ACE and lowering aldosterone levels, ACEI reduces sodium and water retention, thereby lowering blood volume load. This helps reduce both preload and afterload, decrease left ventricular ejection resistance, improve cardiac output, and relieve congestion in the lungs and peripheral tissues. Unlike simple vasodilators, ACEI improves hemodynamics without causing significant reflex tachycardia, allowing heart rate to remain stable while circulation improves.

In terms of protecting heart structure, ACEI slows ventricular remodeling and reduce myocardial hypertrophy and fibrosis [10]. This helps maintain normal ventricular shape and compliance, delaying the decline in ejection fraction. Slower remodeling also lowers the risk of arrhythmia and sudden death, while improving exercise tolerance and quality of life. Long-term use has been proven to reduce the hospitalization rate and all-cause mortality among patients with heart failure.

ACEI also reduces the breakdown of bradykinin, leading to higher levels in the body. Bradykinin promotes the release of nitric oxide (NO) and prostaglandins, which dilate blood vessels, improve endothelium-dependent relaxation, and support microcirculation. It also has anti-inflammatory and anti-fibrotic effects, helping to limit structural damage in the heart and blood vessels [11]. This added

mechanism gives ACEI broader protective benefits beyond lowering blood pressure or reducing fluid load.

Overall, ACEI improves symptoms and hemodynamics in the short term, while protecting heart structure and vascular function in the long term. Common examples include enalapril, lisinopril, ramipril, and perindopril.

3.1. Enalapril

Enalapril is one of the earliest and most widely used ACEIs in the treatment of HF. Enalapril is utilized in patients with asymptomatic left ventricular dysfunction because it slows the progression of symptomatic HF and lowers the risk of death [12]. Due to the excessive activation of the RAAS, it triggers a series of harmful reactions, leading to changes in the structure of the heart. ACEIs can prevent adverse cardiac muscle hypertrophy, reduce aldosterone fluid retention, and increase bradykinin levels by reducing degradation, thereby causing vasodilation. Enalapril is mainly recommended for patients who cannot tolerate side effects, which include cough, when treat with ACEIs. Long-term use enalapril can decreased the relative risk of death by 16% in patients with mild or moderate symptoms [12] The active form of enalapril is enalaprilat, which inhibits ACE and lowers the level of angiotensin II. As a result, aldosterone levels decrease, and serum renin levels increase. Therefore, regulation of the RAAS by ACEIs can improve left ventricular function and reduce cardiac remodeling [13].

3.2. Lisinopril

Lisinopril is a competitive ACE inhibitor. It can prevent angiotensin I from converting into angiotensin II [14]. The reduction of angiotensin II leads to a decrease in aldosterone secretion, thereby reducing the reabsorption of sodium by collecting duct and the excretion of potassium. Compared to enalapril and captopril, it has long half-life, not break down in liver, and it is hydrophilic. High dose lisinopril is more effective than low dose in reducing the risk of clinical events. Compared with low dose patients, patients treat with high dose lisinopril have an 8% lower risk of death, a 12% lower risk of death, and a 24% reduction in the number of hospitalizations. Lisinopril is generally well tolerated by patients with HF. The most common side effects include dizziness, headache, low blood pressure, and diarrhea. The probability of adverse reactions is related to the dose, especially low blood pressure and deterioration of renal function. Nevertheless, these events can usually be properly handled by adjusting the dose of enalapril or taking other medications simultaneously [15].

3.3. Ramipril

Ramipril is an effective long-acting angiotensin converting enzyme inhibitor that has long term hemodynamic effects on patients with congestive HF. Ramipril inhibits the synthesis of angiotensin II. This inhibitory effect leads to a reduction in the conversion of angiotensin II. Consequently, both sympathetic nerve activity, and the reabsorption of sodium and water reduce. Additionally, the smooth muscle in small arteries relaxes, thereby lowering blood pressure. ACE is also involved in the breakdown of bradykinin, which is a vasoconstrictor. The increase in bradykinin levels caused by the inhibitory effect of ACE may contribute to the therapeutic effect of ramipril [16].

4. Safety Evaluation

In the treatment of HF, the safety assessment of ACEIs indicates that these drugs are generally well tolerated, and severe side effects are relatively rare, but they may pose a fatal risk. Patients treated with ACEIs increased risk of dry cough, hypotension, dizziness, and hyperkalemia by 2.66, 1.98, 1.46, and 1.24 times, respectively [17]. The most common adverse effect of ACEIs is dry cough. This symptom is more common with perindopril and ramipril, while it occurs less often with enalapril. The cough is usually not related to dose or treatment duration and is believed to be caused by bradykinin-mediated sensitization nerve of airway sensory and increased substance P in the airways

[13]. Other side effects include low blood pressure and high potassium levels, both of which are linked to the inhibition of angiotensin II production. While low blood pressure is relatively common in susceptible individuals, high potassium levels are less frequent in clinical practice [13].

5. Conclusion

Heart failure is a widespread and serious disease caused by various underlying conditions and is strongly influenced by the overactivation of the RAAS. This essay emphasizes the important role of overactivation of RAAS that contributes to hypertension, water and sodium retention, and cardiac structural remodeling. However, ACEI have been proven to be highly effective inhibitors in the treatment of heart failure. ACEI can not only lower angiotensin II levels, reduce aldosterone, and cause vasodilation, lower blood pressure and reduce the burden on the heart, but also alleviate common symptoms such as dyspnea and edema, reduce readmission rates, and prolong patient survival.

Nevertheless, several limitations remain. ACEI are not without risks. Their side effects include coughing, hypotension, hyperkalemia, and rare but severe angioedema. This might limit its use in some patients. Furthermore, heart failure itself is a multifactorial disease, and its complexity cannot be completely resolved by drug treatment alone.

Therefore, future research should continue to explore combination therapies that can complement the achievements of angiotensin-converting enzyme inhibitors, especially those strategies that combine angiotensin-converting enzyme inhibitors with new drug classes or non-pharmaceutical intervention measures. Furthermore, there remains space for research to explore individualized approaches to minimize adverse reactions, such as hypotension and hyperkalemia. This can be improved by closely monitoring blood pressure and electrolyte levels and adjusting the dosage of drugs or combining diuretics when necessary to enhance safety and efficacy.

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