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Analysis of methods for heart failure

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Abstract. Heart Failure (HF) is one of the major causes of death from various heart diseases and is a common complex clinical syndrome. HF has a high incidence and its 5-year survival rate is similar to that of patients with malignant tumors, which has a serious impact on the quality of life of patients and has become a major public health problem of worldwide concern. At this stage, the clinical treatment of HF is still mainly based on drug therapy. As clinical research progresses, more and more new HF therapeutic drugs are being introduced one after another, new uses of drugs are being discovered and clinical options for drug use are becoming more and more diverse. The drug therapy for HF is also changing from monotherapy to multi-target and multi-mechanism combined mode of action. Innovative mechanical therapy products are also bringing new strategies to the treatment of HF. This article reviews the medication treatment and device implantation strategies for the clinical treatment of HF.

Keywords: heart failure, medication, device treatment.

1. Introduction

Heart Failure (HF) is relatively complex clinical condition in which ventricular contraction or filling is impaired by structural or functional abnormalities of the heart and is one of common cardiovascular diseases in clinical practice, accounting for 32% of all deaths worldwide [1]. Patients with HF are characterized by weakness, dyspnea, and fluid retention as the main symptoms. At present, traditional drugs such as ACEI and ARB are available. However, the therapeutic effect is limited. In recent years, many innovative drugs such as ARNI, SGLT2i, and a new soluble guanylate cyclase stimulator, vilisicam, have been introduced. Innovative devices such as cardiac contractility modulators (CCM) have also been developed. The clinical options are becoming more diverse as more effective therapeutic agents and treatment strategies are being explored for this disease. Therefore, this article reviews the therapeutic agents and strategies for HF.

2. Medication treatment

The goal of drug therapy is not only to improve the patient's symptoms, but more importantly to target the mechanisms of myocardial remodeling, prevent and delay the development of myocardial remodeling.

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2.1. Diuretics

In the 1940s, diuretics were introduced to treat CHF, and as of today, these drugs still have indispensable roles to play in the treatment of this disease. Diuretics allow water and sodium retention to be corrected quickly and promote improvement in clinical symptoms, but adverse phenomena such as hyponatremia and hypokalemia are more likely to occur during treatment and long-term mortality does not improve [2]. It has been found that in HF, the secretion of antidiuretic hormone is increased and activates the RASS system and sympathetic nervous system, which subsequently decreases cardiac output, diminishes renal function, and ultimately causes repeated volume overload [3]. The selective vasopressin V2 receptor antagonist, tolvaptan, has significantly altered therapeutic outcomes in correcting fluid retention due to its unique drainage and sodium preservation effects, and alternating or combining with tab diuretics reduce the incidence of hyponatremia.

2.2. β-blockers

Beta-blockers selectively bind to β-adrenoceptors and block neurotransmitters and catecholamines, thereby reducing their agonistic effects on β-receptors, which in turn can block the activity of RAAS, improve the diastolic function of the heart and anti-arrhythmic effects.

The CIBIS-IIHF trial found a 34% and 32% reduction in all-cause mortality and risk of hospitalization, respectively, in patients with ischemic or non-ischemic moderate or severe HF [4]. The Australian-American Cavidiello carvedilol trial reported that in 415 HF patients with ischemic cardiomyopathy, treatment with carvedilol significantly improved all cardiac function parameters, along with a 26% reduction of all-cause mortality and hospitalization risk [5].

2.3. ACEI and ARB

Angiotensinogen, produced by the liver, is the initial substance in RAAS. Renin, which is secreted by parietal cells, converts angiotensinogen into angiotensin. The disruption of RAAS eventually leads to further deterioration of cardiovascular and renal diseases. Multiple trials have shown that RAAS blockers are beneficial in the treatment of cardiovascular diseases, and ACEI and ARB are popular cardiovascular medications. It was found that ACEI enalapril treatment significantly reduced all-cause mortality, cardiovascular death, or hospitalization for worsening HF in patients with ischemic and non-ischemic mild to moderate HF (NYHA class II-III). The ELITTE-II trial randomized groups to control the effect of losartan versus captopril treatment suggested that losartan reduced the overall mortality, death and/or hospitalization due to worsening HF [6]. ARBs are particularly suitable for patients who cannot take ACEI preparations because of cough or edema caused by ACEI application. With numerous clinical studies on antagonizing neuroendocrine hormone hyperactivation in the treatment of HF, ACEI or ARBs + β-blocker regimens have reduced HF morbidity and mortality and rehospitalization rates.

2.4. Direct renin inhibitors (DRI)

The DRI aliskiren inhibits RAAS at its source. Theoretically reducing angiotensin II (Ang II) production more effectively than ACEI, it can block the effects of RAAS more effectively and eliminate the Ang II accumulation effect of ARBs, i.e, it has a synergistic effect on RAAS inhibition in combination with ARBs. 2016 American College of Cardiology published The ATMOSPHERE trial investigated the clinical efficacy of aliskiren, a DRI in combination with enalapril compared with enalapril alone, enrolling patients with HF, randomized in a 1:1:1 pattern into three groups, i.e., aliskiren group, enalapril group, and enalapril + aliskiren group [7]. It was found that no significant difference is rate of cardiovascular death or HF hospitalization in patients with either aliskiren alone, enalapril alone or aliskiren in combination with enalapril, but the combination of aliskiren and enalapril resulted in increased significantly with the combination of hypotension and hyperkalemia.

2.5. Aldosterone receptor antagonists

Aldosterone receptor antagonists can be divided into two types, one selective, with eplerenone as the main drug, and the other non-selective, with spironolactone and ambrisentin as the main drugs. The

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RALES clinical trial study found that the aldosterone antagonist-spironolactone further improved survival by approximately one-third in patients with HF already treated with ACEI and Tab diuretics [8]. Li explored the effect of enalapril combined with spironolactone CHF treatment, including 114 patients with CHF. It indicated that the clinical effect of the combination of enalapril and spironolactone in the treatment of CHF was significant, and the blood gas index and cardiac function index could be significantly improved [9]. As an aldosterone receptor antagonist applied in the treatment of HF, it can block the aldosterone effect, inhibit myocardial remodeling and improve the long-term prognosis of HF.

In 2014, the Guidelines for the Diagnosis and Treatment of HF in China, published by the Chinese Society of Cardiovascular Diseases, used the combination of three drugs, ACEI + β-blocker + aldosterone receptor antagonist, as a regimen for the treatment of patients with CHFr EF.

2.6. Genetically recombinant human B-type natriuretic peptide (RHBNP)

Nesiritide is a RHBNP that promotes natriuresis, blocks RAAS, and has a vasodilating effect on arteries and veins, similar to BNP secreted by the human body, and was approved by the US FDA in 2001 for AHF. The VMAC study randomized 489 patients with acute decompensated congestive heart failure (ADHF) with dyspnea at rest to nesiritide, nitroglycerin, or placebo on top of standard therapy [10]. The results showed that after 3 h of administration, the nesiritide group significantly reduced the patients' PCWP compared with the nitroglycerin group or placebo, and significantly improved the patients' dyspnea symptoms compared with placebo. After 24 h of administration, patients in the nesiritide group showed a more important reduction of PCWP, but tdyspnea symptoms did not improve, and the degree of improvement in systemic status was slightly better. The results of the ADHERE National Registry of Acute Decompensated HF showed that in-hospital mortality was significantly lower in patients receiving nesiritide injections within the first 24 h of AHF than in patients receiving positive inotropes (milrinone or dobutamine phentermine) and similar to those of patients treated with nitroglycerin [11].

2.7. ARNI

The drug combination of enkephalinase inhibitors and ARBs, ARNI, is currently represented by sacubitril-valsartan, which is a salt complex consisting of two components, sacubitril and valsartan, combined in a 1:1 molar ratio. It acts through enkephalins and the renin-angiotensin-aldosterone system. Thus, sakubril valsartan can inhibit or even reverse cardiac remodeling by suppressing excessive activation of RASS on the one hand, and restore neurohumoral homeostasis by significantly enhancing the natriuretic peptide system on the other. The combined effect of the two drugs counteracts the increase in adrenomedullin, Ang II, bradykinin and endothelin levels caused by enkephalinase inactivation, so that the two drugs complement each other to better inhibit vasoconstriction, reduce water and sodium retention, improve myocardial remodeling, and reduce hospitalization and long-term morbidity and mortality in HF patients. the PROVE-HF study showed that sacubitril-valsartan in HIFrEF patients rapidly reduced natriuretic peptide levels and maintained a steady decline, and that long-term treatment for 12 months consistently improved left atrial remodeling in patients with HF. In the EVALUATE-HF study, sacubitril-valsartan was shown to be effective in improving left atrial remodeling in patients with heart failure after one month of treatment. In a study conducted in an animal model, sacubitril-valsartan was found to significantly improve left function and atrial structure in patients with AF combined with heart failure compared with ARB [12]. Currently, HF guidelines all recommend sacubitril-valsartan as a cornerstone of HFr EF treatment, and sacubitril-valsartan can be used for in-hospital initiation of therapy in patients with primary HFr EF, in combination with β-blockers and aldosterone antagonists to constitute a new combination regimen..

2.8. Sodium-glucose co-transporter protein 2 inhibitor (SGLT2i)

SGLT2i is a novel hypoglycemic agent. SGLT2 is located almost entirely of the proximal tubule of kidney and is responsible for the reabsorption of glucose filtered from the glomerulus; SGLT2i reduces blood glucose levels by decreasing the reabsorption of glucose in the urine. Due to its unique glucose-lowering mechanism, the drug also has the effects of lowering blood pressure, reducing body mass,

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lowering urinary protein and uric acid levels. SGLT2i has many advantages in the treatment of cardiovascular diseases, reducing ventricular load, improving cardiac metabolism, inhibiting cardiomyocyte (Na+)/(H+) exchange, and reducing cardiac fibrosis.

In the cardiovascular field, the therapeutic status of SGLT2 inhibitors has further increased.In 2019, the ESC/EASD published guidelines for diabetes/prediabetes and cardiovascular disease recommend type 2 with combined atherosclerotic cardiovascular disease (ASCVD) or high/very high cardiovascular risk Glucose-lowering drugs are recommended for patients with T2DM. The 2021 ESC Guidelines, include SGLT-2i for the first time as a Class I recommendation in the base treatment regimen for HFrEF. It is used in combination with sarcobalide valsartan, β-blockers and aldosterone antagonists in patients with decompensated HF to form a new regimen for modern HF treatmentx. Compared to conventional ACEI+ARB+BBs therapy, it would have substantially reduced patient mortality, hospitalization rates, and was accompanied by an additional 1.4-6.3 years of survival (based on age 50-70 years). A clinical trial using a quadruple combination of "ARNI+BBs+MRA+Vilisicam" found a 59% reduction in all-cause mortality [13].

2.9. Guanylate cyclase activator (s GC)

Velisicam is a novel s GC agonist that promotes guanosine cyclophosphate (c GMP) production, improves myocardial and vascular function, delays LV remodeling, and prevents or even reverses LV hypertrophy. The addition of vilisicab to standard therapy for HF further reduces the incidence of adverse cardiovascular events and is an important complement to pharmacological therapy for HF. The VICTORIA trial was published in 2020 and 5,050 patients with HFr EF were recruited in the study and treated both with standard therapy plus viliximab or placebo. It showed a significant reduction in hospitalizations and cardiovascular deaths in HF treated with viliximab after 3 months, confirming the availability and reliability of vilisicab in the treatment of HFr EF [14].

3. Device treatment

In recent years, an increasing number of clinical trials have confirmed that device therapy further reduces mortality and greatly improves patients' quality of life and prognosis based on pharmacological treatment, such as cardiac resynchronization therapy (CRT) CCM, etc.

3.1. CRT

The efficacy of CRT has been confirmed by clinical trials and is usually used in patients with CHF with reduced LVEF (≤35%) and wide QRS intervals [15]. New advances in CRT technology in recent years are mainly left ventricular quadrupole leads and left ventricular multipoint pacing techniques, which can create multiple different pacing vectors, capture a larger area of myocardium, improve intraventricular synchronization effects, make left ventricular contraction more coordinated, and thus optimize hemodynamics and improve LVEF; and can lower the left ventricular pacing threshold, increase left ventricular electrode stability, and improve CRT response rates [16].

3.2. CCM

Compared with conventional CRT, CCM treatment can be applied to patients with narrow QRS wave groups, bridging the gap of conventional CRT for patients with narrow QRS wave groups [17]. Overall, CRT patients represent only 1/3 of all HF patients, and about 25% of them are "non-responders", who do not benefit from CRT. CCM can be used in patients with narrow QRS wave groups. CCM is recommended for CHF patients with class II-III cardiac function, LVEF <35%, and narrow QRS wave group, CCM offers new hope for CHF patients and fills a gap in the traditional CRT treatment of patients in the narrow QRS wave group. In a study of CCM reversal of myocardial remodeling [18], 30 heart failure patients (60±11 years, 80% male, NYHA ≥ class III, LVEF<35%, QRS<120ms) who underwent CCM implantation were evaluated for differences from baseline values observed by real-time 3D cardiac ultrasound at 3 months after the procedure. The results showed significant reversal of LV remodeling, improved myocardial contractility throughout the LV wall, including areas away from the CCM

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stimulation target, and improvement in NYHA class and 6MWT, indicating that CCM enhanced overall and local LV contractility, including areas away from the stimulation target, contributing to reversal of LV remodeling and sustained improvement in systolic function.

3.3. Mitral and tricuspid valve clamping

Both acute and chronic mitral regurgitation can cause a dramatic increase in left ventricular volume load, leading to left ventricular insufficiency. The new COAPT trial, a randomized, prospective study of patients with HF combined with functional mitral regurgitation (MR), applied a mitral valve clamping (Mitra Clip) system for percutaneous mitral valve repair with better clinical outcomes and a good safety profile than conventional pharmacological therapy. Zhou et al showed that over 2000-2016 mitral valve interventions were indicated for people with severe disease, the in-hospital mortality rate decreased by 56. 5%, and was significantly associated with improved prognosis. In particular, Mitra Clip procedures increased by 84.4% per year from 2013-2016, resulting in a significant reduction in length of hospitalization [19]. Recent studies have also found that the Mitral Regurgitation System is the leading transcatheter technique for the treatment of MR and is a safe procedure with a very low rate of adverse events compared to mitral valve surgery for intermediate to high risk or secondary MR [20]. Recently, a fourth generation was introduced that is easier to operate the device, reduces the rate of complications, and can even treat complex lesions. And with the increasing maturity of mitral valve interventions represented by the Mitra Clip, interventions on the tricuspid valve are now also on track, with increasing evidence supporting the safety and efficacy of using the Mitra Clip system on the tricuspid valve.

3.4. Mitral and tricuspid valve clamping

LVEF-preserved HF accounts for a progressively higher proportion of all HF, but many treatment challenges remain, particularly in patients with intractable HF. Two atrial shunt devices have been used with initial success, including the interatrial shunt device (IASD) and the V-Wave device, both of which are implanted in the atrial septum to reduce left atrial pressure by shunting, thereby reducing clinical symptoms due to pulmonary stasis.Preliminary results from a study of patients who received second-generation valveless V-Wave shunt implants showed that the V-Wave shunt remained patent and stenosis-free in all cases at 1-year follow-up, with significant improvements in 6 min walking distance [21]. Yi et al [22] evaluated the risks of shunt devices (ISDs) for the treatment of HF in terms of hemodynamic effects. A comprehensive analysis showed that the intraventricular shunt device was effective in reducing PCWP, increasing cardiac output and 6MWD with no significant adverse effects on right heart pulmonary pressures. Although the short- to mid-term efficacy of atrial bypass devices has been confirmed by clinical trials, there is still a need for research with bigger sample numbers and longer follow-up times to confirm the long-term effectiveness.

4. Conclusion

With the in-depth development of clinical research in the field of HF treatment, the drug therapy for HF has also changed from monotherapy to multi-target and multi-mechanism combined mode of action. In the process of HF drug use research, there are still some scientific issues to be further explored, such as the interaction between different types of drugs, the effect of combined drug use, the duration of various drugs, the order of administration and human tolerance to drugs, etc. , which need to be explored in more comprehensive and in-depth clinical trial studies. More novel drug combinations and new drugs, such as combination drugs and eutectic drugs, need to be further promoted and applied. In the future, the treatment of HF patients will be based on the original treatment plan, according to the different etiologies and comorbidities of patients, as well as individual drug response, the combination of drugs with different mechanisms of action, and hopefully, through the synergistic effect of drugs, reduce adverse reactions, increase patient compliance, so that HF patients can obtain more clinical benefits and improve the quality of life. In recent years, HF treatment devices have made tremendous progress in technology and methods, which have benefited more and more HF patients, but each device has its own drawbacks, and the best treatment device should be selected according to the clinical characteristics and

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economic conditions of patients. Drug therapy is still the cornerstone and remains an important and critical measure to improve the quality of life and prolong survival, while more optimal drug therapy and combined with individualized device implantation will be the future direction of treatment for HF patients.

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