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Update: Acute Heart Failure (VI)

Drug Therapy for Acute Heart Failure

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ABSTRACT

Acute heart failure is globally one of most frequent reasons for hospitalization and still represents a challenge for the choice of the best treatment to improve patient outcome. According to current international guidelines, as soon as patients with acute heart failure arrive at the emergency department, the common therapeutic approach aims to improve their signs and symptoms, correct volume overload, and ameliorate cardiac hemodynamics by increasing vital organ perfusion. Recommended treatment for the early management of acute heart failure is characterized by the use of intravenous diuretics, oxygen, and vasodilators. Although these measures ameliorate the patient's symptoms, they do not favorably impact on short- and long-term mortality. Consequently, there is a pressing need for novel agents in acute heart failure treatment with the result that research in this field is increasing worldwide.

Tratamiento farmacológico en la insuficiencia cardiaca aguda

Palabras clave:
Tratamiento farmacológico
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Servicio de urgencias
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RESUMEN

La insuficiencia cardiaca aguda es una de las causas de hospitalización más frecuentes y continúa conllevando dificultades para la elección del mejor tratamiento para mejorar la evolución clínica del paciente. Según lo indicado por las guías internacionales, en cuanto los pacientes con insuficiencia cardiaca aguda llegan al servicio de urgencias, el enfoque terapéutico habitual tiene como objetivo la mejoría de los signos y síntomas, corregir la sobrecarga de volumen y mejorar la hemodinámica cardiaca aumentando la perfusión de los órganos vitales. El tratamiento recomendado para tratar de manera inmediata la insuficiencia cardiaca aguda se caracteriza por el uso de diuréticos intravenosos, oxigenoterapia y vasodilatadores. Aunque estas medidas alivian los síntomas del paciente, no tienen una influencia favorable en la mortalidad a corto y largo plazo. Por consiguiente, hay una necesidad acuciante de nuevos fármacos para el tratamiento de la insuficiencia cardiaca aguda, lo que hace que la investigación en este campo aumente en todo el mundo.

INTRODUCTION

Acute heart failure (AHF) is one of the main reasons for hospitalization worldwide. The treatment of chronic heart failure is well defined in the guidelines and has been demonstrated to improve life expectancy in affected patients.[1,2] However, for AHF, diuretics, oxygen, and current vasodilators are widely used but have not been shown to reduce mortality. Moreover, there are few large trials on the treatment of AHF in emergency departments (ED) and recommendations in contemporary guidelines are only supported by low levels of evidence.[1,2]

Nevertheless, it is currently well recognized that the first step in the management of AHF is early management in the ED.[3,4]

The current approach for patients with AHF in the ED aims to improve the patient's signs and symptoms, correct volume overload, and increase end-organ perfusion and hemodynamic status, conteracting the neurohormonal hyperactivation that is the main physiopathologic mechanism of the disease (Figure 1). It has been demonstrated that an aggressive and appropriate approach to the management of AHF is useful to improve patient outcomes.[5,6] Currently, traditional drug therapy is characterized by the use of diuretics, oxygen, and vasodilators, which remains the cornerstone of the early management of AHF.[7,8]

Despite the earlier initiation of therapy, even when aggressive, mortality in patients with AHF is still very high, demonstrating the need to improve outcomes through the use of new therapeutic strategies.[9,10]

DIURETICS

Diuretics still represent the cornerstone of AHF therapy. The current international guidelines consider intravenous (i.v.) loop diuretics as first-line therapy for patients with AHF.[2,3,11] This approach aims to improve congestion,[12] but evaluation of its

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Abbreviations

AHF: acute heart failure
ED: emergency department
i.v.: intravenous
NTG: nitroglycerin

efficacy in prolonging survival in AHF has been limited to randomized clinical trials.[13] Furosemide, torasemide, and bumetanide are the most commonly used diuretics, and the former is the most widely used in AHF patients. These drugs have different catabolic mechanisms: furosemide is mainly eliminated through the kidney, while torasemide and bumetanide are mainly eliminated through the liver.[14] Recent studies by López et al[15] in animal models have demonstrated that torasemide, but not furosemide, has an inhibitory effect on aldosterone activity, which leads to decreased fibrotic remodeling in myocytes. Moreover, it has been postulated that torasemide may have a different effect on sympathetic system activation.[16]

Due to the greater bioavailability of diuretics through intravenous rather than oral administration, i.v. administration is recommended in AHF patients, which allows the diuresis process to start 30 min to 60 min after administration. Similar to morphine, i.v. loop diuretics have an initial venodilating effect, which decreases pulmonary congestion before the onset of diuresis.[17,18] There is still debate on the dose-response relationship with i.v. diuretics, and often the initial dose is empirical. The guidelines recommend an initial i.v. diuretic dose that equals or exceeds the patient's daily dose in maintenance therapy.[11] The ESCAPE trial[19] analysis demonstrated that there is a dose-dependent morality risk for i.v. diuretics especially with furosemide that excedes 300 mg/day.[19] A single-center study showed that the highest quartile of the daily diuretic dose (> 160 mg) has the highest risk-mortality rate.[20] Peacock et al[21] showed that diuretics could worsen renal function in high doses with consequent poor patient outcomes. However, these data were influenced by different variables (advanced heart failure, renal insufficiency, comorbidities) that increase patient risk for worse outcomes.

In a Cochrane review of 8 clinical trials on AHF of patients randomized to continuous vs bolus loop diuretic administration, those receiving continuous infusion had increased urine output. Because continuous infusion results in a more constant delivery of diuretic to the tubule, it reduces postdiuretic rebound sodium retention and maintains more consistent diuresis.[22] However, recently, the double-blind DOSE (Diuretic Optimization Strategies Evaluation), trial randomized patients to low- or high-dose i.v. furosemide, and continuous vs intermittent i.v. furosemide administration. The results showed a trend for greater symptom relief in the high-dose group, with improvement of volume loss and decreased weight at 72 hours. In the high-dose group, creatinine levels increased, but this did not influence length of hospital stay or survival. Moreover, it was also demonstrated that the efficacy of continuous infusion was similar to that of intermittent bolus therapy.[23]

Thiazides are less active diuretics in the management of AHF. They can be used when AHF patients seem to have an inadequate response to loop diuretics, which often occurs in the case of diuretic resistance[17] (Figure 2). The combination of metolazone with loop diuretics has been demonstrated to be highly effective.[24]

The neurohumoral compensatory mechanism in AHF activated by diuretic treatment with stimulation of the sympathetic nervous system and the renin-angiotensin-aldosterone system

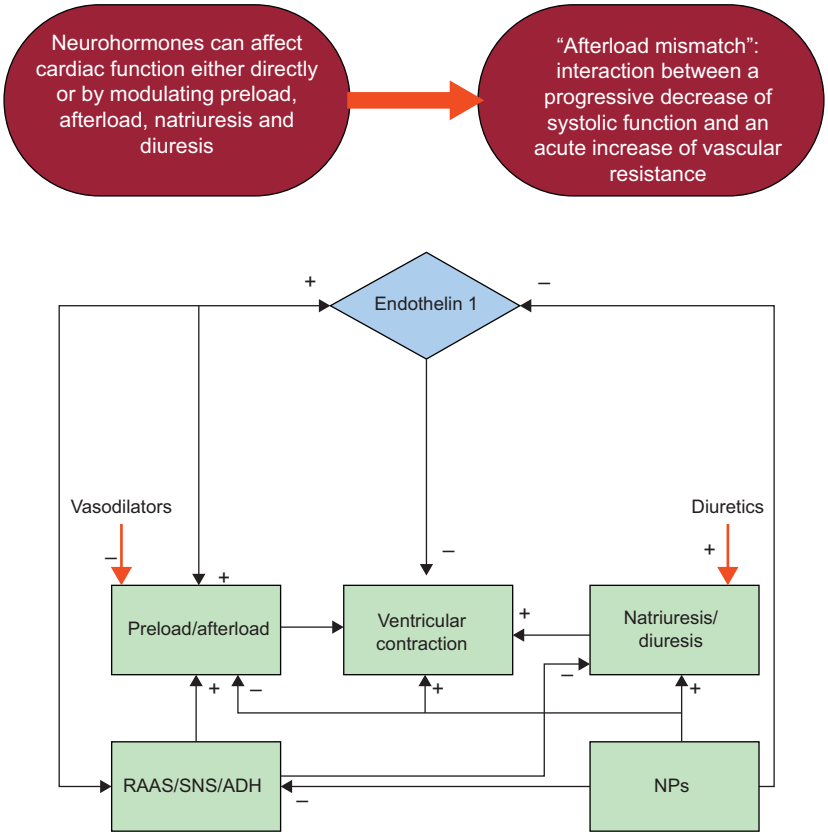

Figure 1. Pathophysiology and treatment of acute heart failure. Actions of diuretics and vasodilators. ADH, antidiuretic hormone; NPs, natriuretic peptides; RAAS, renin angiotensin aldosterone system; SNS, sympathetic nervous system.