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SYMPOSIUM. HEART FAILURE

Organ protection possibilities in acute heart failure☆

M. Montero-Pérez-Barquero[a,*], **J.L. Morales-Rull**[b]

[a] *Servicio de Medicina Interna, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC)/Hospital Reina Sofía, Universidad de Córdoba, Córdoba, Spain*
[b] *Unidad de Insuficiencia Cardiaca, Servicio de Medicina Interna, Hospital Universitario Arnau de Vilanova, Región Sanitaria de Lleida, Lleida, Spain*

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Abstract Unlike chronic heart failure (HF), the treatment for acute HF has not changed over the last decade. The drugs employed have shown their ability to control symptoms but have not achieved organ protection or managed to reduce medium to long-term morbidity and mortality. Advances in our understanding of the pathophysiology of acute HF suggest that treatment should be directed not only toward correcting the hemodynamic disorders and achieving symptomatic relief but also toward preventing organ damage, thereby counteracting myocardial remodeling and cardiac and extracardiac disorders. Compounds that exert vasodilatory and anti-inflammatory action in the acute phase of HF and can stop cell death, thereby boosting repair mechanisms, could have an essential role in organ protection.

PALABRAS CLAVE
Insuficiencia cardiaca aguda;
Daño orgánico;
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Posibilidades de organoprotección en la insuficiencia cardiaca aguda

Resumen A diferencia de la insuficiencia cardiaca (IC) crónica, el tratamiento de la IC aguda no ha cambiado en la última década. Los fármacos empleados han demostrado controlar los síntomas, pero no han conseguido una protección orgánica ni una reducción de la morbimortalidad a medio y largo plazo. Los avances en el conocimiento de la fisiopatología de la IC aguda sugieren que el tratamiento debe dirigirse no solo a corregir las alteraciones hemodinámicas y a conseguir un alivio sintomático, sino sobre todo a prevenir el daño orgánico, contrarrestando el remodelado miocárdico y las alteraciones cardiacas y extracardiacas. Las moléculas que en

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* Corresponding author.
E-mail address: fm1mopem@uco.es (M. Montero-Pérez-Barquero).

la fase aguda de la IC puedan ejercer acciones vasodilatadoras y antiinflamatorias —y que sean capaces de detener la muerte celular, favoreciendo los mecanismos de reparación— podrían tener un papel esencial en la protección orgánica.

Background

Heart failure (HF) is a significant health problem that affects 15 million patients in Europe and 5 million in the United States.[1,2] HF results in an extremely high consumption of healthcare resources,[1,3] which is mainly due to the high rate of hospitalizations for acute HF (AHF). More than a million patients each year in the United States are hospitalized for HF, with a mean cost per hospitalization of $19,000.[4] In addition to the significant and constantly rising rate of annual readmissions, AHF has high mortality. The predictions are far from optimistic, with an even greater increase in the coming years, due to the aging of the population and an increase in predisposing factors for HF, such as arterial hypertension and ischemic heart disease.[1,5–7]

The treatment for AHF has essentially remained unchanged in recent decades. Most clinical trials performed with new drugs have failed to reduce morbidity and mortality, probably because of insufficient understanding of the pathophysiology and pharmaceutical mechanisms of action.[8]

Pathophysiology of acute heart failure

The pathophysiology of AHF syndrome is complex and difficult to interpret, partly due to the lack of experimental models. Given the diversity of the clinical presentations, there are probably various pathophysiological mechanisms involved in the disease.[9] During episodes of AHF, cardiac dysfunction occurs, which includes acute damage to the myocardium, with subsequent remodeling, along with systemic and pulmonary circulation dysfunction. In addition to hemodynamic impairment and neurohormonal activation, there is inflammation and oxidative stress in the genesis of the myocardial, renal and hepatic injury, as well as myocardial remodeling.[10–12]

Neurohormonal activation involves various systems and signaling pathways, such as the renin–angiotensin–aldosterone system (RAAS), the sympathetic nervous system, endothelin-1, the adrenomedullin and natriuretic peptides.[13]

The inflammatory reaction mainly includes the immune response activation, the increase in inflammatory mediators (e.g., tumor necrosis factor, interleukin-1, interleukin-6 and a new HF biomarker of the family of interleukin-1 receptors known as ST2), complement system activation, antibody production and overexpression of histocompatibility and adhesion compounds.[14,15]

Oxidative stress results from an excess of molecules that react with nitric oxide and that lead to the production of toxic substances (e.g., peroxynitrite and isoprostane), which increase purine catabolism, with a subsequent increase in serum uric acid and the release of myeloperoxidases by the activated neutrophils and monocytes.[16]

The abnormalities observed in the myocardium during AHF are related to the progression of myocardial dysfunction and structural abnormalities, such as myocardial hypertrophy, cardiomyocyte apoptosis, depression of myocardial contractility with inhibition of the response capacity of the cardiomyocytes to beta-adrenergic stimulation, growth of fibroblasts, fibrosis and remodeling. It has been proposed that a significant loss of cardiomyocytes occurs during AHF episodes (by necrosis), as well as abnormalities in the architecture of the extracellular myocardial matrix (remodeling). Evidence of the loss of cardiomyocytes includes the increase in plasma troponin, which takes place during exacerbation episodes, in the absence of acute coronary syndrome.[17–19]

Renal dysfunction has an important role in the pathophysiology of AHF. The following mechanisms have been proposed to explain the relationship between the 2 conditions (Fig. 1):

(1) *Hemodynamic abnormalities*. The kidneys are sensitive to hemodynamic changes, such as increased venous pressure and reduced cardiac output. In patients with AHF, the increase in central venous pressure and intraabdominal pressure are important determinants of the increase in creatinine levels. The reduction in cardiac output is another determinant of renal impairment in HF.[20]
(2) *Sympathetic hyperactivity*. The kidneys are richly innervated by sympathetic efferent nerve fibers, and the sympathetic renal impulses are markedly increased in HF. The sympathetic stimulation decreases renal blood flow, through vasoconstriction of the renal artery, and stimulates the release of renin by juxtaglomerular cells.[21]
(3) *RAAS*. Angiotensin II can initially cause vasoconstriction of the efferent arteriole, boosting glomerular filtration despite the low renal blood flow during AHF. However, RAAS activation has long-term adverse effects on the kidneys, including the induction of inflammatory phenomena, fibrosis, increased oxidative stress and endothelial dysfunction. Antagonism of these pathogenic mechanisms is the basis of the protective effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists.[22].
(4) *Adenosine release*. The release of adenosine can contribute to renal dysfunction, as occurs when high doses of furosemide are administered.[23]
(5) *Inflammation and oxidative stress*. Inflammation can play an important role in cardiorenal interaction.