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Update: Acute Heart Failure (II)

Pathogenesis and Clinical Presentation of Acute Heart Failure

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ABSTRACT

Acute heart failure constitutes a heterogeneous clinical syndrome, whose pathophysiology is complex and not completely understood. Given the diversity of clinical presentations, several different pathophysiological mechanisms along with factors triggering circulatory decompensation are involved. This article discusses the available evidence on the pathophysiological phenomena attributed or/and associated with episodes of acute heart failure and describes different clinical profiles, which, from a clinical perspective, constitute a key element for therapeutic decision-making.

Patogenia y presentación clínica de la insuficiencia cardiaca aguda

Palabras clave:
Insuficiencia cardiaca aguda
Fisiopatología
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Tratamiento

RESUMEN

La insuficiencia cardiaca aguda es un síndrome clínico heterogéneo, cuya fisiopatología es compleja y no se conoce por completo. Dada la diversidad de formas de presentación clínica, intervienen en ella varios mecanismos fisiopatológicos diferentes, junto con factores que desencadenan una descompensación circulatoria. En este artículo se comenta la evidencia existente sobre los fenómenos fisiopatológicos atribuidos y/o asociados a los episodios de insuficiencia cardiaca aguda y se describen diferentes perfiles clínicos que, desde una perspectiva clínica, constituyen un elemento clave para la toma de decisiones terapéuticas.

ACUTE HEART FAILURE: A COMPLEX CLINICAL SYNDROME WITH DISTINCT PATHOPHYSIOLOGIES

Acute heart failure (AHF) can be defined as a heterogeneous syndrome of signs and symptoms of new-onset or gradual/rapidly worsening heart failure (HF), requiring urgent therapy.[1,2] AHF constitutes a clinical syndrome with a complex and, more importantly, not completely understood pathophysiology.[3–5] Given the diversity of clinical presentations, several different pathophysiological mechanisms along with factors triggering circulatory decompensation are involved.[3–5] This article discusses the available evidence on pathophysiological phenomena attributed or/and associated with episodes of AHF

From the pathophysiological perspective, the a priori condition of AHF is heart dysfunction (including acute myocardial damage and remodeling) accompanied by dysfunction in systemic and pulmonary vasculature (with the involvement of endothelial dysfunction), which eventually lead to severe acute hemodynamic abnormalities. Their origin is not completely understood, but several generalized phenomena are postulated to be involved (neurohormonal activation, inflammatory process, oxidative stress). The contribution of dysfunction of other organs (kidneys, liver) is also suggested. Factors triggering AHF may include ischemia, hypertension, arrhythmias, noncardiac comorbidities, and administered drugs, etc.

NEUROHORMONAL ACTIVATION, INFLAMMATORY ACTIVATION AND OXIDATIVE STRESS

Circulatory decompensation is characterized by the presence of the following phenomena[3–5]: neurohormonal activation,[6–11] inflammatory activation,[12–14] and oxidative stress.[15–17] All these 3 entities, although obviously distinct, have several common features.

Firstly, they can be detected at the tissular level (within myocardial tissue and tissues of other affected organs, eg, kidneys), but also, due to their generalized nature, they may be tracked in peripheral circulation. Secondly, their role during hemodynamic stress is primarily adaptive, as they allow the increased effort performed by heart and circulatory system to be combatted, but only for a limited time. When they are preserved, they become maladaptive and detrimental, augmenting the circulatory

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Abbreviations

AHF: acute heart failure
HF: heart failure
WHF: worsening heart failure

insufficiency and impairing generalized homeostasis. Thirdly, they are involved in the progression of heart dysfunction, both during the acute phase of circulatory decompensation, and also afterwards, as their influence far exceeds beyond the episode of AHF and contributes to a steady progression of chronic HF. Finally, they are considered as strong predictors of poor outcome, being prognosticators of increased short- and long-term mortality as well as of an increased risk of recurrent hospitalizations due to subsequent episodes of AHF.

Neurohormonal activation includes the activation of the following systems and related signaling pathways: *a)* renin-angiotensin-aldosterone system[6]; *b)* sympathetic nervous system (with the depletion of the parasympathetic nervous system and associated abnormal cardiopulmonary reflex control, ie, attenuated baroreflex, augmented central and peripheral chemoreflexes)[7]; *c)* arginine vasopressin (along with copeptin, the C-terminal segment of pre-pro-vasopressin as a stable and reliable surrogate for vasopressin)[8]; *d)* endothelin-1[9]; *e)* adrenomedullin,[10] and *f)* the system of natriuretic peptides.[11]

Inflammatory reaction includes predominantly an activation of innate immune response, an increased expression of proinflammatory mediators (such us tumor necrosis factor, interleukin-1, interleukin-6, ST-2), activation of the complement system, autoantibody production, and overexpression of major histocompatibility complex molecules as well as adhesion molecules.[12–14]

Oxidative stress is associated with an excess of reactive oxygen species, which, for example, react with nitric oxide, disrupt physiologic signaling, and lead to the production of toxic and reactive molecules (peroxynitrite, isoprostane, aminothiols), and increased purine catabolism, which in turn increases xanthine oxidase activity and subsequently serum uric acid levels and also induces an augmented release of myeloperoxidase by activated neutrophils and monocytes.[15–17]

Most importantly, all these aforementioned pathomechanisms are the primary mechanisms of a proven role in the progression of HF predominantly in its chronic/stable phase. They have been demonstrated during episodes of AHF in observational/descriptive studies but there is no major mechanistic proof in acute settings.

MYOCARDIAL DYSFUNCTION

Circulatory decompensation always occurs in patients with abnormal function of the myocardium, but heart dysfunction demonstrated in patients with AHF varies in its character (systolic/diastolic dysfunction, left/right heart), triggering factor (ischemia, inflammation, hypertension) and clinical course (rapid, gradual worsening), etc.[4,5,18] Systolic function of the left ventricle may vary from normal to severely impaired and be accompanied by diastolic dysfunction or mitral regurgitation. An important clinical problem is right ventricular dysfunction, which usually complicates the dysfunction of the left heart. All these abnormalities affect the symptoms of AHF are associated with unfavorable clinical outcomes.[3,4,18]

Abnormalities seen within the myocardium during AHF are most likely due to the afore-mentioned phenomena: *a)* neurohormonal activation; *b)* inflammatory activation, and *c)* oxidative stress. They are related to progressed myocardial dysfunction and associated structural abnormalities, including cardiomyocyte hypertrophy, cardiomyocyte apoptosis, depressed myocardial contractility, inhibited cardiomyocyte responsiveness to β-adrenergic stimulation, fibroblast growth, fibrosis, and remodeling, to name but a few.

Regardless of the underlying molecular mechanisms and triggering factors, episodes of AHF are postulated to be associated with marked cardiomyocyte loss (necrosis) and dynamic changes in the architecture of the myocardial extracellular matrix (remodeling). Cardiomyocyte damage can be reflected by confirmation of high levels of circulating cardiac troponins.[19] For example, in the ADHERE registry, detectable cardiac troponins were confirmed in 75% of patients hospitalized due to AHF, and carried poor prognosis.[20] The triggering/acceleration of myocardial remodeling during AHF may be reflected by an increased expression of molecules belonging to 2 groups of molecules involved in the regulation of the dynamically changing status of extracellular matrix, ie, matrix metalloproteinases (MMPs) degrading fibrillar collagens and tissue inhibitors of metalloproteinases (TIMPs),[21] as well as galectin 3, a β-galactoside–binding lectin produced mainly by macrophages, involved in the fibroblast activation and tissue fibrosis.[22]

ENDOTHELIAL DYSFUNCTION

Acute heart failure is also characterized by generalized endothelial dysfunction (some authors call this pathology endothelitis). This dysfunction may be due to an imbalance within neurohormonal, inflammatory and oxidative milieu in the circulation and endothelial cells, as well as due to other unidentified factors, which clinically may cause: *a)* myocardial hypoperfusion, reduced coronary flow and ischemic dysfunction; *b)* increased vascular stiffness and impaired arterial distensibility further aggravating myocardial damage; *c)* vasoconstriction within the systemic and pulmonary circulation, resulting in an increased left and right ventricular afterload; *d)* endothelin-related secondary increased sympathetic drive and catecholamine release, and *e)* renal dysfunction, reflected mainly by the reduced sodium excretion, but also associated with other abnormalities.[23]

OTHER ORGAN DYSFUNCTION (KIDNEYS, LIVER)

Importantly, heart dysfunction itself is only one element of the complex pathophysiology of AHF, and other abnormalities within vasculature and peripheral pathomechanisms involving other body organs (eg, kidneys, liver, endothelium, lungs) play a critical (if not always dominant) role.[3–5,24,25]

Renal dysfunction plays an important role in the pathophysiology of AHF, but its origin is not completely understood. In addition, the pathophysiology of the contribution of renal dysfunction as a factor aggravating or triggering an episode of AHF, as well as contributing to the further progression of HF and poor outcomes, remains unclear.[3,4,25,26]

Renal dysfunction includes decreased glomerular filtration rate (assessed using different glomerular filtration rate [GFR] formulas based on the measurement of circulating creatinine, cystatin C), abnormal tubular function (reflected by high levels of neutrophil gelatinase-associated lipocalin [NGAL], kidney injury molecule 1 [KIM1] in both peripheral blood and urine) and inadequate