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HEART FAILURE – MULTISYSTEM SYNDROME

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Rezumat

Insuficienţa cardiacă este un sindrom clinic complex cu evoluţie severă care în ciuda tratamentului complex şi complet conduce la distrucţie miocardică cu progresia bolii. Insuficienţa cardiacă a fost clasificata in funcţie de fracţia de ejecţie (FE) în: insuficienţa cardiacă cu FE păstrată şi insuficienţa cardiacă cu FE redusă.

Insuficienţa cardiacă cronică progresează prin scăderea continuă a eficienţei functiei de pompă, remodelare miocardică şi dilataţie cardiacă, retenţie de hidrosalina (sindrom cardio-renal) modulată de axa cardio-renală pe calea mecanismelor neurohormonale: sistemul nervos simpatic, sistemul renină-angiotensină-aldosteron, sistemul arginin-vasopresina, endotelina, peptidele natriuretice.

Cuvinte cheie: *sisteme neurohormonale, remodelare cardiacă, retenţie de apă şi Na*

Abstract

Heart failure is a complex clinical syndrome with severe evolution that, despite complex and complete treatment, leads to progressive myocardial damage with subsequent disease progression. Heart failure has been differentiated according to ejection fraction (EF) into heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF).

Chronic heart failure progresses through a continuous decrease in pumping efficiency, myocardial remodeling and cardiac dilatation, and water and sodium retention (cardiorenal syndrome), which are modulated by the cardiorenal axis via neurohormonal mechanisms: the sympathetic nervous system, renin-angiotensin-aldosterone system (RAAS), arginine-vasopressin, endothelin, and natriuretic peptides.

Keywords: *neurohormonal systems, cardiac remodeling, water and sodium retention*

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Heart failure is a syndrome characterized by decreased systemic perfusion resulting from cardiac pump dysfunction and abnormalities in the peripheral vascular system, and neurohormonal activation plays a significant role in the progression of heart failure. Heart failure is not just a disease of the heart, and because of the neurohormonal changes it involves, it becomes a severe systemic disease. The modern concept has redefined heart failure, which is nowadays interpreted as a multiorgan syndrome and affects different cell types having multiple neurohormonal activations, the cardiorenal axis with water and sodium retention. However, the neurohormonal activation explains the heart failure syndrome but does not fully account for the disease progression.

The leading causes of cardiac dysfunction include ischemic heart disease, arterial hypertension, valvular diseases, and cardiomyopathies by various etiologies, including genetic cardiomyopathies, involving proteins with different cellular functions. On the one hand, these abnormalities alter the balance between ventricular ejection capacity and peripheral needs and, on the other hand, cardiac remodeling to compensate for the functional deficit.

Abrupt (e.g., myocardial infarction) or insidious deterioration of cardiac function triggers compensatory mechanisms to counteract the heart's pumping function decline. Neurohormonal activation is currently interpreted as one of the most critical mechanisms favoring the progression of heart failure. The result of neurohormonal activation in heart failure consists in the release of vasoconstrictor and sodium-retaining neurohormones such as angiotensin (ANG) II, norepinephrine, endothelin, adenosine, and arginine vasopressin; these effects are counterbalanced by vasodilator and natriuretic mediators - natriuretic peptides, prostaglandins, bradykinin, and nitric oxide. Therapeutic antagonism of neurohormonal systems, therefore, plays a significant role in heart failure therapy.

Neurohormonal activation in heart failure

Neurohormonal dysfunction is the primary mechanism by which the syndrome progresses. Decreased cardiac output causes activation of aortic, carotid, and cardiac baroreceptors with secondary activation of multiple neuroendocrine systems: noradrenaline, arginine-vasopressin (ADP), plasmatic atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), endothelin, and the renin-angiotensin-aldosterone system (RAAS). Initially, this neuroendocrine response is essential for the short-term recovery of cardiovascular homeostasis, increasing wall stress with the subsequent development of cardiac hypertrophy. Still, the hormonal

response becomes maladaptive in the long term and contributes to myocardial remodeling and the risk of life-threatning arrhythmias. Sustained neurohormonal activation, except for natriuretic peptides, plays a critical role in the progression of heart failure and is responsible for pathogenic mechanisms that lead to the perpetuation and worsening of heart failure. In contrast, natriuretic peptides have a favorable role in heart failure.

In heart failure, the trigger for neurohormonal activation is sympatho-adrenergic activation that initially attempts to restore cardiac output. This activation starts early in SV dysfunction, before the clinical manifestations of heart failure. β-adrenergic and RAAS activation are responsible for maladaptive remodeling and arrhythmogenic risk. Sympatho-adrenergic stimulation *per se* is cardiotoxic and, leads to stimulation of the renin-angiotensin-aldosterone axis and endothelin release. Catecholamine excess results mainly from increased SNS activity in the heart and kidneys and correlates with impaired VS function, wildly beating volume and ventricular preload, and increased plasma norepinephrine levels > 600 pg/ml indicate an unfavorable prognosis.

In heart failure, cardiac output is ensured by circulating catecholamines, and prolonged cardiac hyperactivity of the SNS leads to reduced norepinephrine stores in the failing myocardium. A vicious circle is generated in which compensatory inotropic support is compromised by the effect of circulating catecholamines with increased vascular resistance, increased afterload, compromised cardiac performance, and worsening heart failure. At the cellular level, catecholamine cardiotoxicity is related to the relationship between sympatho-adrenergic activation, apoptosis, and cell necrosis.

The renin-angiotensin-aldosterone system (RAAS) is an essential hormonal cascade that, contributes to fluid balance and blood pressure homeostasis, under normal conditions. The RAAS influences BP by regulating water and salt balance and vasoconstriction; over-activation of the system leads to cellular/tissue remodeling and cardiovascular dysfunction. The major primary effector of RAAS is angiotensin II (ANG II), a potent vasoconstrictor. The alternative pathway produces ANG 1-7 via cleavage of ANG II by ACE 2.

ANG II controls BP regulation through target organ effects and has a significant role in cardiac remodeling and fibrosis by being involved in inflammatory processes, activating inflammatory cells and adhesion molecules, modulating cytokines that mediate cardiac remodeling, and modulating fibroblasts and macrophages.

ANG II aggravates neurohormonal activation by stimulating norepinephrine and aldosterone secretion. ANG II induces aldosterone secretion in the adrenal gland, directly affecting the myocardium by inhibiting nitric oxide synthase, with inflammation, fibrosis, and apoptosis of cardiac myocytes.

The independent effects of aldosterone on extracellular volume cause sodium retention and potassium excretion in the distal convoluted tubule. In addition, aldosterone causes myocardial and vascular fibrosis, direct vascular injury, baroreceptor dysfunction, and alters the action of norepinephrine on the myocardium.

Through all these actions, β-adrenergic and RAAS activation in heart failure are responsible for maladaptive remodeling and arrhythmogenic risk. Neurohormonal antagonists are an essential component of heart failure therapy. Using β blockers

increases the density and sensitivity of β adrenergic receptors, increasing heart failure patients' survival. However, the use of β-blockers is indicated with caution depending on the degree of heart failure, administration, and the patient's chronotropic incompetence (inability to increase heart rate during exercise). In clinical practice, there are ACE inhibitors (ACEI), angiotensin receptor blockers (ARB), angiotensin receptor neprilysin inhibitors (ARNI), sacubitril/ valsartan, mineralocorticoid receptor antagonists, and direct renin inhibitors.

Plasma arginine-vasopressin (PAV) is elevated in patients with congestive heart failure. PAV contributes to disease progression through the V1a and V2 receptor pathway by various mechanisms: vasoconstriction with increased systemic vascular resistance, increased afterload, myocardial hypertrophy, coronary vasoconstriction with reduced coronary flow and cardiac contractility (V1a receptors), and fluid retention, edema, and hyponatremia with angiotensin II involvement (V2 receptors). In contrast, V1a antagonism produces vasodilatation, and V2 antagonism is associated with aquaresis and electrolyte excretion. Numerous selective vasopressin antagonists (vaptans) are currently used for the treatment of hyponatremia and volume overload.

The natriuretic peptide system is known to counteract and mitigate the adverse effects of RAAS and SNS in heart failure.

Atrial myocytes secrete ANP in response to atrial wall stretch due to increased intravascular volume, endothelin, angiotensin, and arginine-vasopressin. Ventricular BNP is secreted due to cardiac wall stretch caused by volume overload. CNP is secreted in the brain, chondrocytes, and cytokines in endothelial cells and has no natriuretic action.

In addition to natriuretic action, natriuretic peptides have recently been shown to have immunomodulatory effects on polymorphonuclear cells and macrophages, ROS and/or nitric oxide production, promote phagocytosis, interfere with the secretion of proinflammatory cytokines, and favor or attenuate tissue fibrosis/necrosis processes. In addition, natriuretic peptides stimulate endothelial nitric oxide and reduce platelet aggregation. Thus, natriuretic peptides are essential regulators of inflammatory mediators in heart failure.

Heart arrhythmias are an aggravating factor in the progression of heart failure.

Arrhythmogenesis in heart failure may be related to autonomic nervous system imbalance with predominance of SNS activity in both atrial and ventricular arrhythmias, with multiple mechanisms involved. SNS has arrhythmogenic effects that may trigger atrial and/or ventricular ”adrenergic” arrhythmias in susceptible patients (ischemic heart disease, cardiomyopathies). Increased parasympathetic activity can trigger vagotonic

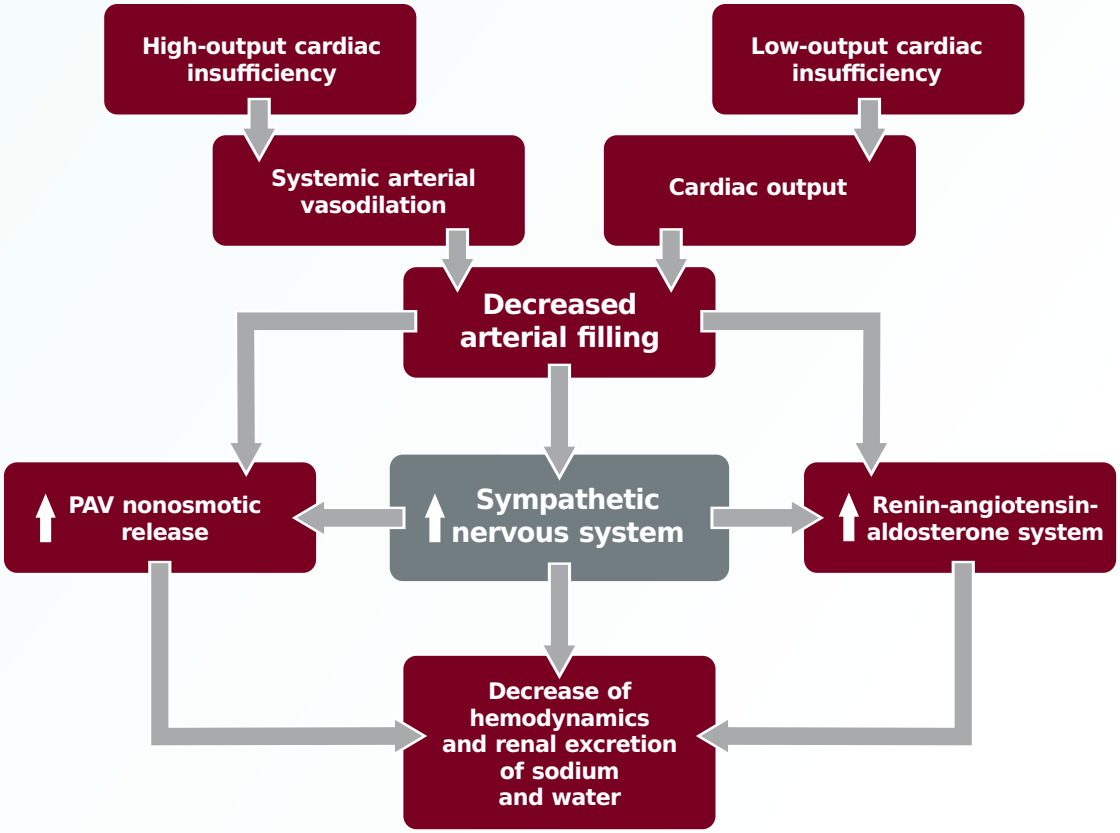

Figure 1. *Pathophysiology of decompensated heart failure*

Pro-remodeling molecules
Vasoactive substances (norepinephrine, angiotensin II)
Aldosterone
Growth factors (transforming growth factor β)
Cytokines (cardiotrophin 1)
ROS, PPAR γ Endothelin Some growth factors: TGFα, TGFβ, TNFα
Anti-remodeling molecules
Natriuretic peptides Vasoactive substances (NO, prostacyclin, angiotensin 1-7, bradykinin)
Glucocorticoids
Growth factors (insulin -like growth factor 1)
Cytokines (tumor necrosis factor α)
PPAR α

Table 1. *Biological agents involved in cardiac remodeling*
ROS = reactive oxygen species; PPAR = peroxisone proliferator-activated receptor

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arrhythmias: paroxysmal atrial fibrillation, Brugada syndrome, and idiopathic ventricular fibrillation.

Maintaining the balance between sympathetic and parasympathetic activity is necessary in all arrhythmogenic diseases, including heart failure.

Hormonal release in heart failure is triggered as a compensatory mechanism, and the effects of these mediators on cardiac contractility, heart rate, peripheral vascular resistance, diuresis, and natriuresis initially succeed in maintaining cardiac output. Neurohormonal mechanisms initially favor improved perfusion by increasing ventricular preload, myocardial contractility, and heart rate; thus, the symptoms of heart failure are delayed. The activation of SNS, RAAS, and PAV favors maintaining cardiovascular balance at the onset of heart failure and in the short term. Still, the bioactive molecules produced by activating these systems (catecholamines, angiotensin II, aldosterone, and PAV) become toxic to the heart above a certain level. The inhibitory effect of arterial baroreceptors on SNS and RAAS is decreased in both forms of heart failure. A decrease in arterial filling produces this effect by reducing cardiac output (low output heart failure) or arterial vasodilation (high output heart failure). In addition, neurohormonal mechanisms are potent mediators of oxidative stress, inflammation, and cell death and modulate endothelial dysfunction, fibrosis, and cardiac remodeling.

The imbalance between vasoconstrictor and sodium-retaining effects and vasodilator and natriuretic effects has a significant role in worsening heart failure and renal function, and the mechanisms involved in the progression of heart failure are intertwined, worsening each other and creating a spiral leading to myocardial damage.

Chronic activation of numerous vasoactive hormones (catecholamines, angiotensin II, endothelin, vasopressin) produces cardiac remodeling, fibrosis, myocardial and endothelial dysfunction, and water and salt retention. It worsens ventricular function and hypoperfusion that occur in both low and high output heart failure. Thus, angiotensin II-induced hyperadrenergic and hyperaldosteronic status and SNS hyperactivity precipitate the clinical symptoms of heart failure and disease progression. Blocking these molecules with β-blockers, ACE inhibitors, ARBs, aldosterone antagonists, vaptans, ARNI-neprilysin, combat the unfavorable effects of neurohormonal activation and restore the imbalance between vasoconstrictor and vasodilator agents.

The progression of heart failure is favorised by multiple mechanisms and systems. Prolonged neurohormonal activation and sodium and water retention induce cellular changes in heart failure with cardiac

remodeling/dilation. Prolonged exposure of the hypertrophied heart to elevated levels of circulating hormones produces cardiac dysfunction with clinically manifested heart failure, functional hypoxia, metabolic disorders, renal salt and water retention, cardiac dilatation and mitral insufficiency, pulmonary hypertension, and left ventricular failure.

The cellular mechanisms by which heart failure progresses are mainly ventricular remodeling with initial ventricular hypertrophy and then cardiac dilatation, myocardial and interstitial fibrosis, and myocardial ischemia. Neurohormonal antagonists favor the stabilization of symptoms in heart failure and the regression of VS remodeling. However, the remission of heart failure is limited, and symptoms may recur.

Myocardial ischemia causes the progression of heart failure syndrome by altering systolic/diastolic function.

Myocardial remodeling is a fundamental mechanism in the progression of heart failure, a consequence of prolonged neurohormonal activation and permanent volume overload. It is characterized by myocyte loss and myocardial hypertrophy, inflammation, alteration of the extracellular matrix, fibrosis, metabolic abnormalities, and mitochondrial dysfunction.

Cardiac remodeling is generally defined as a change in ventricular structure, volume, and geometry caused by complex molecular, cellular, interstitial, and genomic changes caused by various heart injuries (ischemia, autoimmunity, volume, and pressure overload).

Remodeling results from cardiac overload or injury and determines the progression and worsening of heart failure. It is mainly influenced by the hemodynamic load and neurohormonal activation, which plays a key role in this process.

Many biological agents are involved in cardiac remodeling.

1. RASS *activation occurs in all types of ventricular remodeling*. ANGII synthesis is ”up-regulated”, and ANG II produces cardiomyocyte hypertrophy of vascular smooth muscle cells and fibroblast proliferation, cytotoxic effect on cardiomyocytes, with cell necrosis and fibrosis. It stimulates aldosterone secretion and collagen synthesis by fibroblasts.
2. *The sympathetic nervous system is an essential contributor to the progression of cardiac remodeling*. The remodeled and deficient heart has anatomic and functional changes in sympathetic innervation and adrenergic receptors. Betareceptor density is decreased, and response to endogenous and exogenous catecholamines is reduced; catecholamine hyperstimulation produces myocyte hypertrophy and myocyte necrosis, with loss of myocytes and worsening remodeling.
3. *Endothelin is a potent vasoconstrictor* with actions that lead to progressive remodeling: it stimulates the release of renin and aldosterone, proliferation of vascular smooth muscle cells and fibroblasts, and increases the expression of some proto-oncogenes.
4. *Natriuretic peptides* inhibit the release of norepinephrine from nerve endings and its vasoconstrictive actions (experimentally), suppress renin formation, stimulate aldosterone secretion, and reduce central SNS activation. In chronic heart failure, the normal function of atrial pacing by distension or volume is adversely affected, and ANP release is thus decreased.

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Vasodilator systems, mainly natriuretic peptides, are surpassed by the effects of vasoconstrictor systems due to ventricular disorder, creating the conditions for progressive cardiac remodeling and progression of heart failure.

The phenotype of cardiac remodeling refers to ventricular hypertrophy and cardiac dilatation as myocardial response to injury or hemodynamic stress. In heart failure, remodeling starts with cardiac hypertrophy and almost invariably progresses to changes in cardiac volume and geometry (sphericity), depression of contractility, or myocardial compliance with cardiac dilatation.

Once remodeling begins, a vicious circle is established in which the remodeling process perpetuates cellular and molecular changes. The effect of hypertrophy is wall-stress normalization, which has beneficial results on VS function, but in the long term, pathological hypertrophy contributes to VS disorder.

Ventricular hypertrophy leads to the progression of heart failure through diastolic and systolic myocyte disorder, interstitial fibrosis, reduced coronary reserve, and consequent myocardial ischemia as a result of changes in capillary-to-myocyte ratio.

Increased left ventricular mass index is related to volume overload and cardiac preload and is associated with increased myocardial transmural pressure and increased SV mass.

The effect of hypertrophy is the normalization of wall stress, which has beneficial results on VS function, but in the long term, pathological hypertrophy contributes to VS disorder. Ventricular hypertrophy leads to a progression of heart failure through diastolic and systolic myocyte disorder, reduced coronary reserve, and consequent myocardial ischemia as a result of altered myocyte/capillary ratio and interstitial fibrosis. VS hypertrophy is associated with reduced capillary density, increased ischemic events - including angina or infarction - systolic and/or diastolic disorder, arrhythmias, and sudden death.

Cardiac dilation

The changes in the failing myocardium involve cardiac myocytes, with myocardial necrosis and cardiomyocyte apoptosis, progressive alteration of extracellular martix and contribute over time to cardiac dilation and contractile disorder.

The cellular event that defines decompensating hypertrophy is cardiomyocyte degeneration, with apoptosis and necrosis precipitated by the exact neurohormonal mechanisms that stimulate compensatory hypertrophy. At this stage, there is a loss of cardiac myocytes and their replacement by fibrous tissue and cardiac dilatation, decreased contractile performance, cardiac decompensation, and irreversible functional deterioration.bA feature of chronic heart failure is renal retention of sodium and

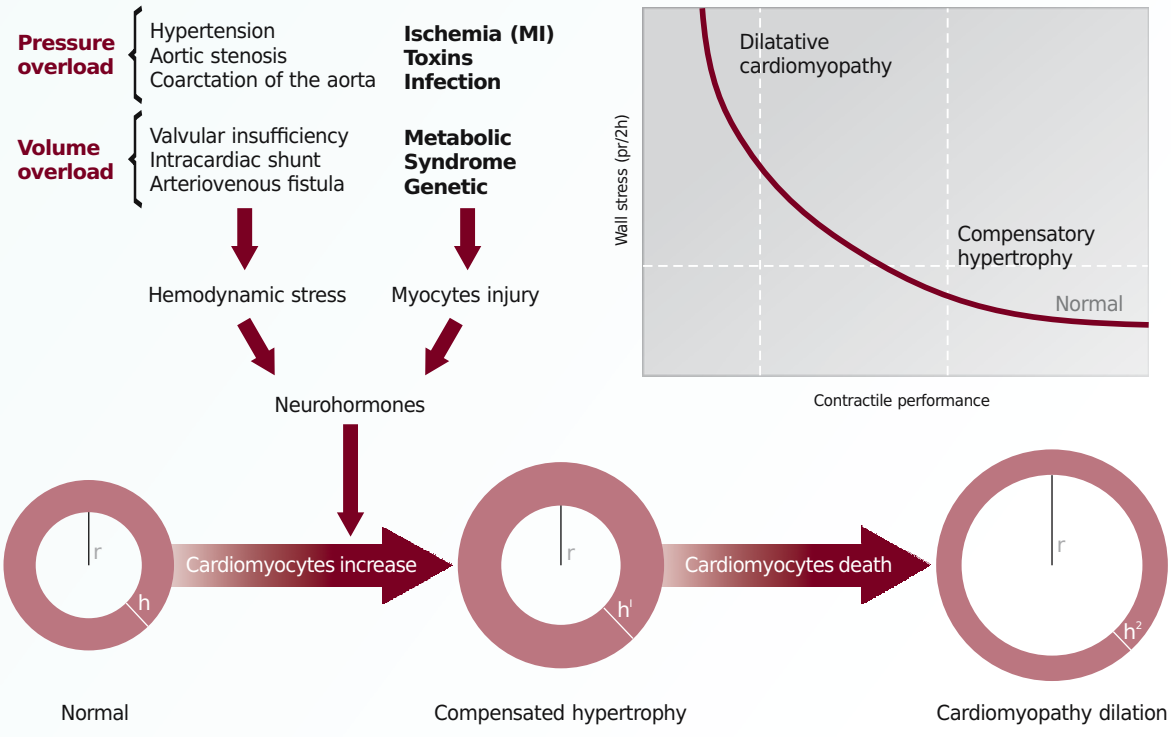

Figure 2. *Development and progression of heart hypertrophy*

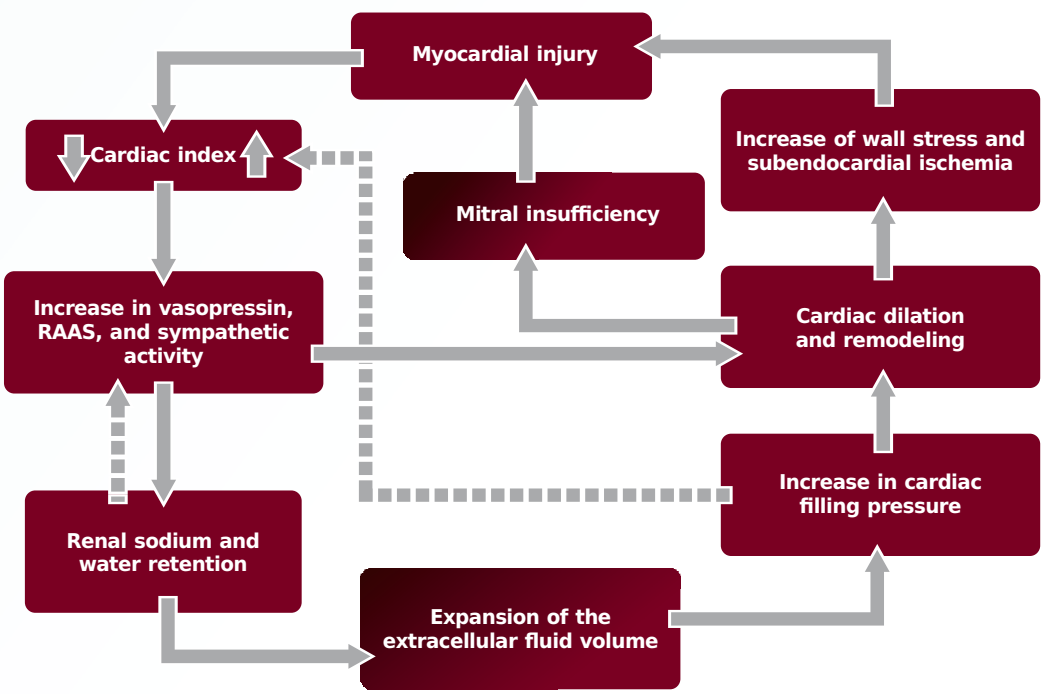

Figure 3. *Myocardial injury leads to cardiac remodeling/dilation through neurohormonal activation and Na and water retention*

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water, even in the presence of apparently normal renal function. This retention produces extracellular fluid expansion with persistent volume overload (preload increases), myocardial remodeling with cardiac dilatation, relative myocardial ischemia, and progression of heart failure.

The attenuation of the atrial reflexes and renal function contributes to the mechanism of water and sodium retention in cardiac insufficiency.

Under normal conditions, increased pressure in the left atrium initiates reflexes with favorable effects on renal function, which overcome sodium and water retention by:

- Suppression of antidiuretic hormone release - arginine vasopressin with aqueous diuresis, which vagotomy can abolish (Henry-Gauer reflex).
- Reduced renal sympathetic tone.
- Increased atrial natriuretic peptide.

In chronic heart failure, these mechanisms are overcome by continuous sodium and water retention. The attenuation of atrial reflexes and renal function is associated with the attenuation of renal arterial baroreceptor sensitivity, increased renal sympathetic activity, and increased circulating catecholamines. This results in a vicious circle with edema formation, pulmonary hypertension, and worsening heart failure. Cardiac dilatation produces functional mitral insufficiency over time, contributing to pulmonary hypertension and left ventricular failure.

Mechanism of water and sodium retention in heart failure

Decreased cardiac function in heart failure is associated with activation of neurohormonal mechanisms, sodium and water retention, congestion, and impaired renal function (”renocardiac syndrome”). Sodium and water retention in heart failure is the result of the interaction between the heart and the kidney, which is modulated by the cardiorenal axis via neurohormonal mechanisms: sympathetic SN, RAAS, arginine-vasopressin, and natriuretic peptides.

The physiologic response is altered, and the kidney retains sodium and water by overfilling the venous system, although the total blood volume is increased.

This sequence of events is distinct from the cardiovascular complications that occur in primary renal disease (”renocardiac syndrome”).

In the normal heart, the increased pressure in the left atrium elicits reflexes with favorable effects on renal function by two types of mechanisms:

- Stimulates a feedback system that reduces the release of the antidiuretihormone arginine-vasopressin from the posterior pituitary and reduces renal sympathetic nervous system activity;

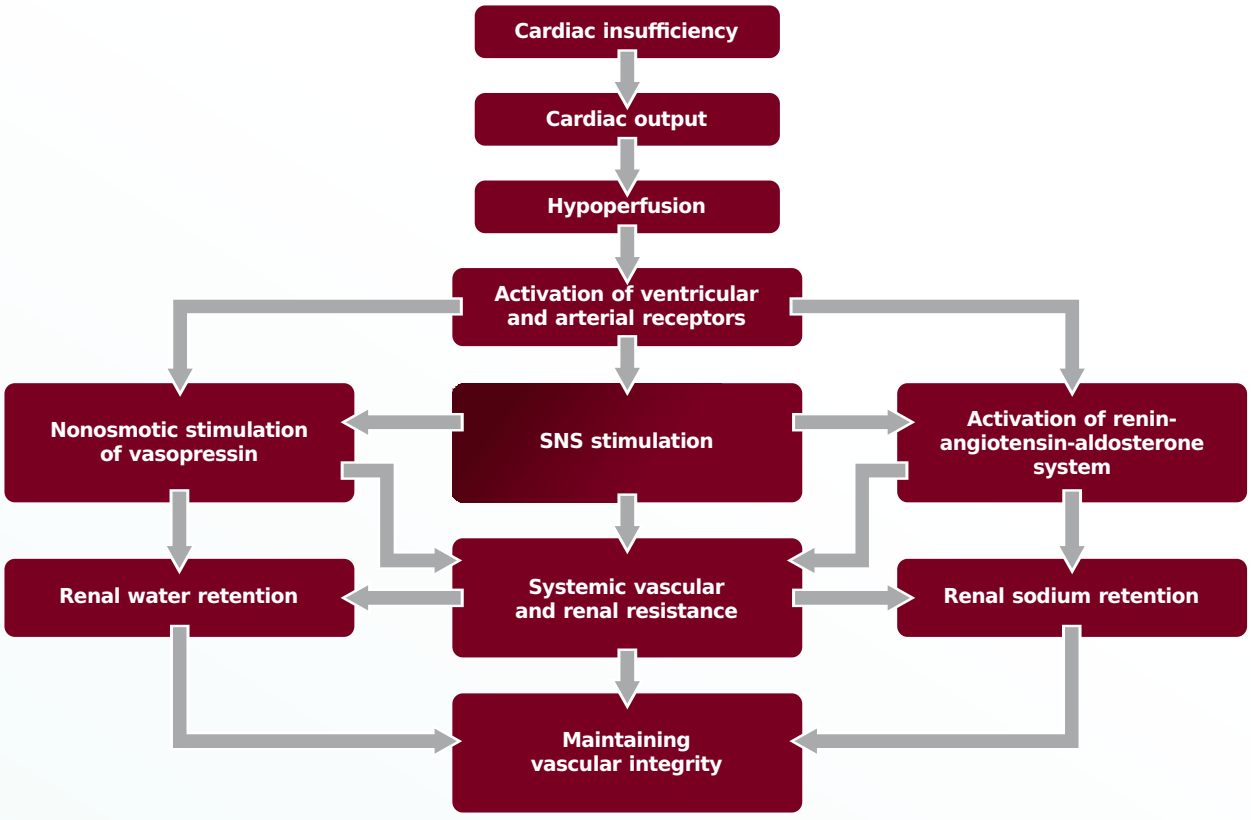

Figure 4. *Water and sodium retention in heart failure*

- Myocardial dilation and stretching cause increased secretion of atrial natriuretic peptide.

The interaction of these mechanisms increases sodium and water excretion and results in the maintenance of total blood volume and the integrity of arterial circulation.

In heart failure, sodium and water retention is triggered by a decrease in cardiac output, which is associated with sodium retention by different mechanisms:

- Disruption of baroreceptor activity;
- Increased sympathetic tone/increased renal β-adrenergic stimulation;
- RAAS activation;
- Nonosmotic release of vasopressin increases vascular resistance and renal reabsorption of water.

This development is correlated with attenuation of atrial reflexes and renal function and altered fluid homeostasis in both low and high output heart failure.

Sympathetic hyperactivity via the renal β-adrenergic stimulation pathway and angiotensin II are the neuroendocrine mechanisms that increase systemic vascular resistance and renal sodium and water retention to restore vascular-arterial filling and maintain circulatory integrity.

ANG II stimulates aldosterone secretion, which is associated with sodium and water retention; the decrease in sodium levels reaching the distal nephron reduces the standard mechanism of ”escape” from aldosterone-induced sodium retention. Thus, ANG II and adrenergic stimulation increase sodium reabsorption in the proximal tubule, directly

affecting the tubular epithelium and indirectly affecting renal vasoconstriction. Aldosterone increases sodium reabsorption in the collecting tubule and induces cardiovascular injury independent of its sodium and water retention effects and BP raising effects. Aldosterone activates mineralocorticoid receptors in non-epithelial tissues, producing oxidative stress, endothelial dysfunction, inflammation, and fibrosis with cardiovascular and renal injury in excess salt. This effect is counteracted by mineralocorticoid receptor blockers (spironolactone, eplerenone).

In the early stages of chronic heart failure, ventricular dilatation is associated with increased BNP (brain natriuretic peptide), which favors maintaining sodium balance (natriuretic and diuretic effect) and suppressing RAAS. Exogenous BNP reduces preload, enhances the effect of loop diuretics, and reduces cardiac fibrosis. In advanced heart failure, the impact of BNP is diminished due to decreased renal perfusion pressure and decreased sodium levels in the distal nephron - the site of action of BNP.

In heart failure, the result of these neurohormonal mechanisms is the retention of sodium and water, which produces congestion, edema formation, and pulmonary hypertension. Thus, all components of the remodeling process participate in the development and progression of heart failure. In this way, the initial compensatory mechanisms produce hemodynamic difficulties with increased cardiac pressor and afterload, cardiac dilatation, cardiac mechanical work, arrhythmias, decreased myocardial relaxation, and exaggerated renal vasoconstriction.

Conclusions

Heart failure is due to a variety of pathologic stimuli, including myocardial infarction, pressure overload, volume overload, and acquired or genetic cardiomyopathies associated with cardiac hypertrophy. In the pathogenesis of heart failure, it participates in many neurohormonal mechanisms that initially contribute to the compensation of the insufficiency.

Prolonged neurohormonal activation with sodium and water retention and cardiac remodeling contribute to the progression of heart failure by multiple mechanisms.

Persistent activation of the neurohormonal system leads to the progression of heart failure through direct effects on the heart and peripheral vascular system:

- the positive chronotropic and inotropic effect of catecholamines;
- vasoconstrictor effects of catecholamines, angiotensin II, and endothelin;
- increased tubular reabsorption of water and sodium;

- remodeling with cardiac hypertrophy and dilatation, with deterioration of cardiac function.

Prolonged sympathetic SN activation in chronic heart failure leads to increased myocardial oxygen demand, promotes intracellular calcium toxicity, and amplifies proliferative effects with hypertrophy, fibrosis, and cardiac remodeling. Thus, the progressive accumulation of imbalances compromises compensatory mechanisms and precipitates myocardial disorder. Each pathophysiological loop aggravates heart failure and leads to new unfavorable developments in myocardial morphology and function.

However, the transition mechanism from cardiac hypertrophy to heart failure is not yet well-defined.

The biology of cardiac remodeling partly explains the limitations of current therapies based on blocking neurohormonal systems and the benefits of invasive procedures (e.g., cardiac resynchronization). Compensated hypertrophy mediated by neurohormonal mechanisms can be inhibited with neurohormonal antagonists.

Conventional medical therapies with ACE inhibitors and β-blockers reduce systolic and diastolic load, block adverse neurohormonal signals, and contribute to the regression of hypertrophy but are associated with a low effect on ventricular remodeling. Initially, ACE inhibitors normalize the wall/volume ratio and reduce end-diastolic VS volume. Still, thereafter, it progressively increases.

Unlike conventional therapy, cardiac resynchronization therapy has advantages related to the regression of cardiac remodeling. Moreover, recent stem cell therapy could attenuate early post-myocardial infarction remodeling.

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