ISSN 2664-8075 (Print) & ISSN 2706-5774 (Online)
South Asian Research Journal of Applied Medical Sciences
Abbreviated Key Title: South Asian Res J App Med Sci

| Volume-7 | Issue-3 | May-Jun- 2025 | **DOI: https://doi.org/10.36346/sarjams.2025.v07i03.005**

Review Article

Pathophysiological Insights into Congestive Heart Failure: From Cellular Mechanisms to Clinical Practice – A Review

Abeer Ameen Mustafa[1*], Rafal Mustafa Tuama[1], Marwa Abdulsalam Kader[1]

[1]Department of Biology, College of Science, University of Tikrit, Iraq

***Corresponding Author:** Abeer Ameen Mustafa
Department of Biology, College of Science, University of Tikrit, Iraq

Article History
Received: 12.05.2025
Accepted: 17.06.2025
Published: 24.06.2025

Abstract: Congestive heart failure (CHF) represents a complex clinical syndrome which results from multiple pathophysiological mechanisms that impair cardiac function and produce systemic symptoms. This review examines all aspects of congestive heart failure development and progression through cellular and molecular and hemodynamic abnormalities. The development of CHF symptoms and multi-organ involvement results from the combined effects of neurohormonal activation and inflammation and oxidative stress and structural cardiac remodeling. The diagnostic process for CHF identification now combines clinical assessment with biomarkers and imaging techniques and hemodynamic evaluation to provide earlier and more precise diagnoses. The current treatment approaches for CHF include pharmacological neurohormonal pathway interventions and lifestyle changes and device-based therapies and surgical procedures that match disease severity and patient characteristics. The development of gene and cell-based treatments together with precision medicine and artificial intelligence applications shows promise for better patient outcomes. The implementation of pathophysiological knowledge in clinical practice through personalized and team-based care approaches leads to the best possible management outcomes. The review emphasizes ongoing challenges and future directions in CHF research and treatment because continued innovation remains essential to decrease the worldwide impact of this common disease.

Keywords: Congestive Heart Failure, Pathophysiology, Neurohormonal Activation, HFrEF, HFpEF.

1. INTRODUCTION

1.1 Definition of Congestive Heart Failure (CHF)

The clinical syndrome of congestive heart failure (CHF) develops from any structural or functional impairment that affects ventricular filling or ejection of blood. The heart fails to deliver enough blood for tissue metabolic requirements which produces symptoms including dyspnea and fatigue and fluid retention [1]. The classification of CHF depends on ejection fraction which results in three categories: heart failure with reduced ejection fraction (HFrEF), preserved ejection fraction (HFpEF) and mildly reduced ejection fraction (HFmrEF) that represent different pathophysiological mechanisms [2].

1.2 Clinical Relevance and Impact on Healthcare

CHF represents a major global public health burden. The disease affects 64 million people worldwide and results in high hospitalization rates and significant morbidity and mortality (GBD 2019 Diseases and Injuries Collaborators, 2020). Heart failure affects 6.2 million American adults while remaining the primary reason for hospital admissions among people aged 65 and older [3].

The economic impact of CHF is equally significant. The total direct and indirect costs of CHF in the United States reached more than $43 billion during 2020 through hospital stays and medication expenses and lost productivity and long-term care needs. The chronic and progressive nature of CHF requires sustained management approaches which combine pharmaceutical interventions with procedural treatments and supportive care [4].

1.3 Purpose and Scope of the Review

The review examines the complete pathophysiological processes of CHF starting from cellular and molecular aspects through organ system effects to clinical presentation. The review demonstrates why understanding these mechanisms remains crucial for better diagnosis and treatment planning and clinical decision support.

2. Epidemiology and Risk Factors

2.1 Global Prevalence and Incidence

The global health challenge of congestive heart failure (CHF) affects 64.3 million people worldwide because of aging populations and better survival rates from acute cardiac events (GBD 2019 Diseases and Injuries Collaborators, 2020). The prevalence of heart failure exists in 1–2% of adults in developed nations while it increases dramatically with advancing age. The United States reported 6.2 million adults received heart failure diagnoses during 2020. The European population exceeds 15 million heart failure cases which generates substantial health problems and financial strain (Figure 1) [5].

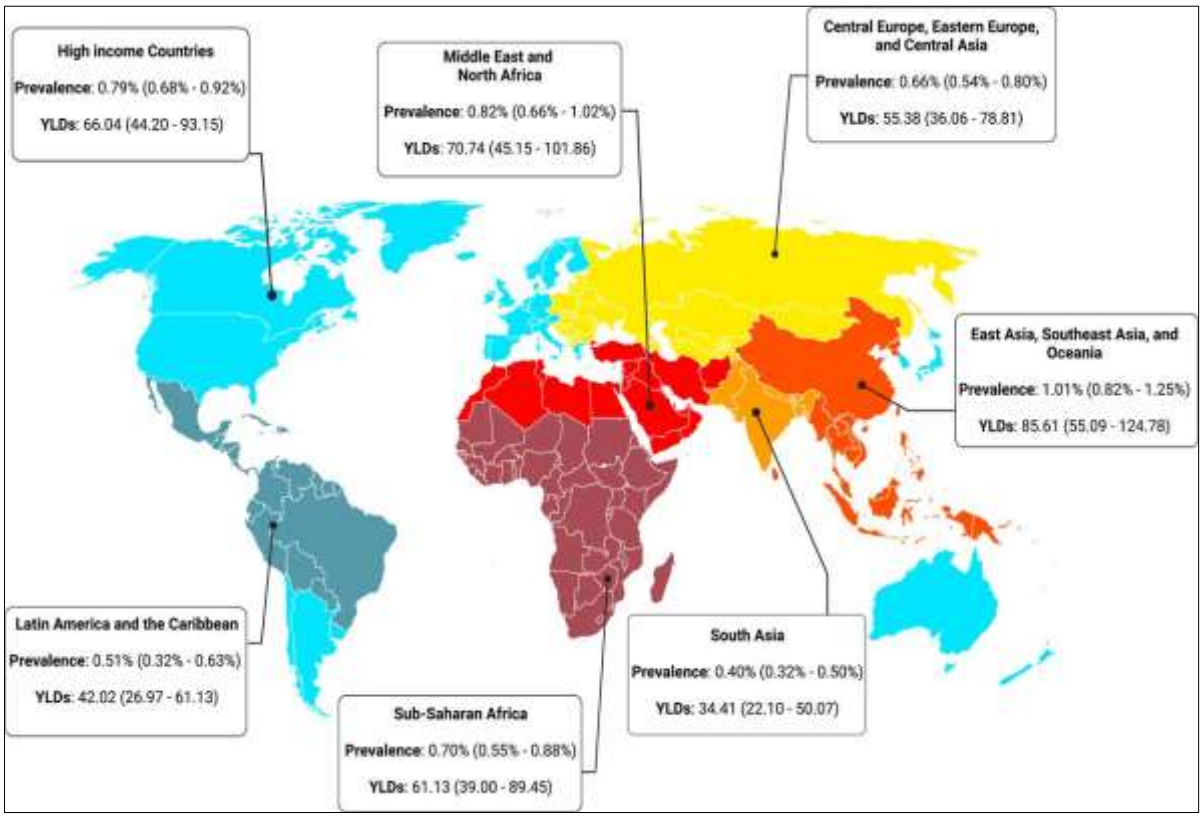

Figure 1: The worldwide distribution of CHF cases, with high prevalence rates in North America and Europe, and increasing rates in low- and middle-income countries

The 5-year mortality rate for this condition remains at approximately 50% which is similar to many cancers. The hospital readmission rates within 30 days of discharge can exceed 25% which reflects both the complexity of care and limitations of current management strategies [6].

2.2 Demographic Trends

The prevalence of CHF grows substantially with age because it affects less than 1% of people under 50 but affects more than 10% of people older than 70. The age-related increase in CHF prevalence stems from the progressive development of cardiovascular diseases and additional health conditions [7].

The presentation and progression of CHF shows different patterns between male and female patients. Men develop HFrEF more often because of ischemic causes whereas women typically show HFpEF symptoms with hypertension and preserved systolic function [8]. The prevalence rates and treatment outcomes of CHF differ between different ethnic groups and geographic locations. The CHF onset occurs earlier in African Americans living in the U.S. and they experience worse outcomes while resource-constrained areas struggle to provide diagnosis and treatment services which negatively impacts survival rates [9].

2.3 Common Risk Factors

The multifactorial syndrome of congestive heart failure (CHF) develops through complex interactions between different risk factors that are modifiable and non-modifiable (Figure 2). Hypertension stands as the leading cause of both HFrEF and HFpEF heart failure because it represents the most significant and influential risk factor [10]. The left ventricle faces continuous pressure stress from hypertension which triggers compensatory ventricular thickening and elevated oxygen needs and eventually results in diastolic heart dysfunction. The development of HFrEF becomes more likely when patients have coronary artery disease (CAD). The heart muscle experiences damage from myocardial infarction which creates both contractile tissue loss and scar tissue formation that ultimately results in systolic heart dysfunction [11].

Diabetes mellitus functions as a fundamental cause of CHF because it creates microvascular problems and insulin resistance and metabolic problems that result in diabetic cardiomyopathy. Obesity functions as an independent risk factor for CHF while making its clinical course worse through its effects on volume overload and systemic inflammation and neurohormonal dysregulation [12]. The combination of fluid retention with anemia and cardiovascular risk factors such as hypertension and diabetes make CKD a complex condition. The combination of tobacco use with excessive alcohol consumption and physical inactivity creates additional cardiovascular stress which speeds up the development of clinical heart failure. The multiple risk factors that exist together create a need for comprehensive preventive strategies in CHF management [13].

Figure 2: Common Risk Factors for Congestive Heart Failure

3. Classification of Congestive Heart Failure

The classification of congestive heart failure (CHF) is essential for understanding its clinical presentation, guiding treatment, and assessing prognosis. The modern classification systems are based primarily on left ventricular ejection fraction (LVEF), which provides insight into the mechanical function of the heart [14]. In addition to LVEF-based categories, CHF is also stratified by functional status using the New York Heart Association (NYHA) classification and by disease progression through the ACC/AHA staging system. These overlapping frameworks reflect the complexity and heterogeneity of heart failure [15].

3.1 Heart Failure with Reduced Ejection Fraction (HFrEF)

The medical definition of Heart failure with reduced ejection fraction (HFrEF) requires left ventricular ejection fraction (LVEF) measurements below 40% (Figure 3). The classical form of systolic heart failure exists as HFrEF because the heart muscle fails to contract effectively (Figure 4) which results in decreased cardiac output [16]. The main pathophysiological characteristic of HFrEF involves reduced contractility which stems from myocardial infarction and dilated cardiomyopathy and other myocardial injuries. The clinical presentation of HFrEF patients includes volume overload symptoms like pulmonary congestion and peripheral edema together with fatigue and exercise intolerance [17].

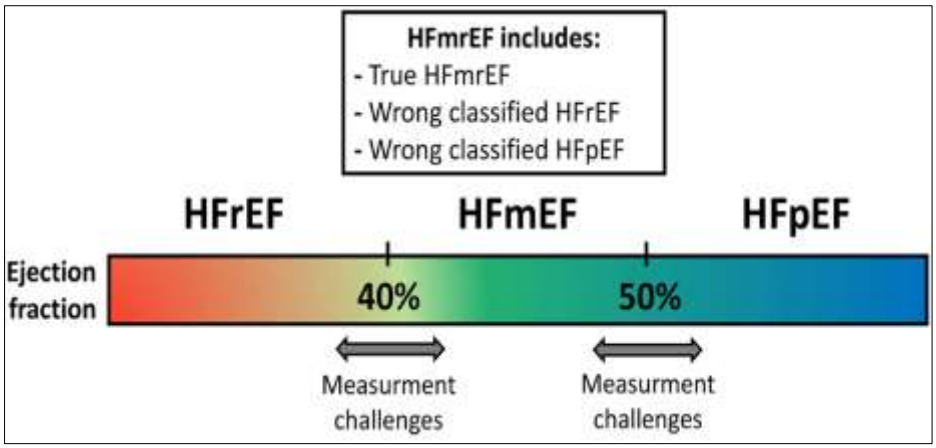

Figure 3: Classifications of congestive heart failure based on ejection fraction

The therapeutic research on HFrEF has produced the most extensive body of knowledge among all heart failure types. Multiple clinical trials have proven that neurohormonal antagonists including ACE inhibitors and beta-blockers and mineralocorticoid receptor antagonists and SGLT2 inhibitors reduce morbidity and mortality in these patients [18].

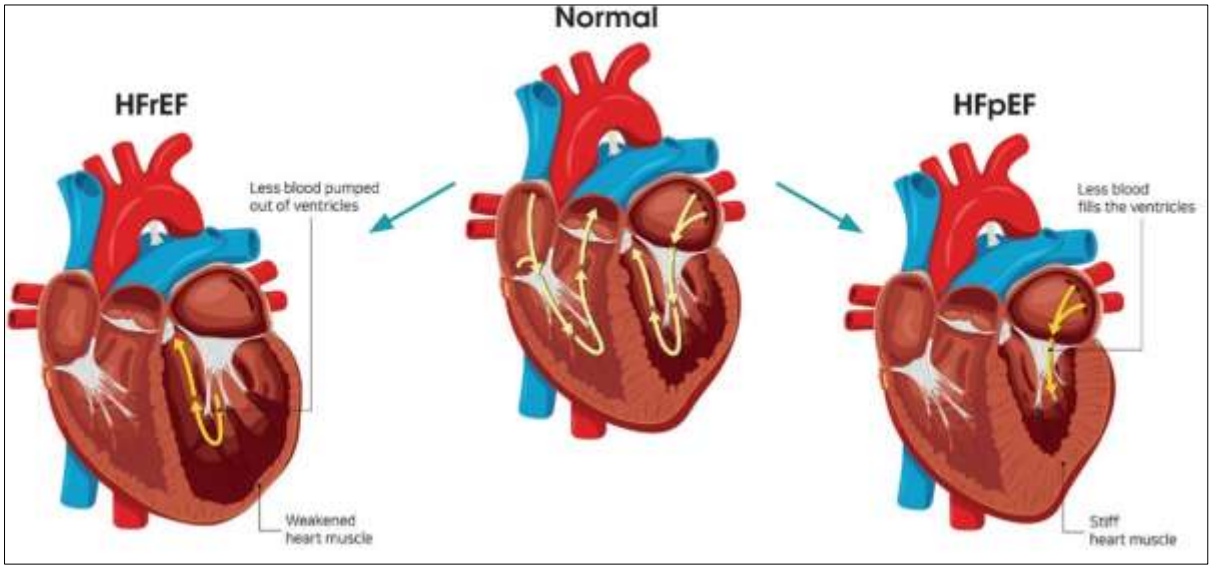

Figure 4: Comparison between HFrEF and HFpEF

3.2 Heart Failure with Preserved Ejection Fraction (HFpEF)

The diagnosis of heart failure with preserved ejection fraction (HFpEF) occurs when LVEF measures 50% or higher (Figure 3) together with heart failure symptoms and diastolic dysfunction evidence (Figure 4). The condition HFpEF affects elderly women more often than men and commonly occurs with hypertension and obesity and diabetes mellitus and atrial fibrillation [19]. The main cause of HFpEF does not stem from systolic dysfunction but from abnormal ventricular relaxation and increased myocardial stiffness which produce elevated left ventricular filling pressures mainly during physical activity [20].

The diagnosis of HFpEF remains difficult because it shows nonspecific clinical indicators and standard echocardiography reveals normal ejection fraction. Research has shown that HFpEF exists as a systemic condition which produces low-grade inflammation and endothelial dysfunction and impaired nitric oxide signaling. The condition used to have few treatment options but recent studies demonstrate that SGLT2 inhibitors along with therapies for comorbidities show promising results [21].

3.3 Heart Failure with Mildly Reduced Ejection Fraction (HFmrEF)

The condition Heart failure with mildly reduced ejection fraction (HFmrEF) shows LVEF values between 41% and 49% (Figure 3) as a newly identified intermediate condition. The medical community previously classified HFmrEF under HFrEF or HFpEF categories until researchers established its unique clinical and pathophysiological characteristics.

The risk factors of HFmrEF patients match those of HFrEF patients because they have ischemic heart disease and hypertension yet their ventricular function shows only slight impairment [22].

The available evidence indicates that HFmrEF patients can benefit from ACE inhibitors and beta-blockers similar to HFrEF patients but the therapeutic benefits fall between these two conditions. The condition HFmrEF exists as a transitional phase of heart failure development or recovery because patients can evolve into either HFpEF or HFrEF based on disease progression and treatment outcomes [23].

3.4 New York Heart Association (NYHA) Functional Classification

The NYHA classification serves as an established functional tool which organizes heart failure severity through symptom intensity and their effects on physical activity. The classification system consists of four distinct classes. The NYHA classification system divides patients into two groups based on physical activity limitations where Class I patients have no limitations and Class II patients experience slight limitations. The classification system includes Class III for patients who experience major daily activity restrictions and Class IV for patients who experience symptoms while resting [24].

The NYHA classification system continues to serve both clinical practice and research purposes despite its subjective nature. The NYHA classification system helps doctors track disease progression and decide which patients qualify for advanced treatments including implantable devices or heart transplantation [25].

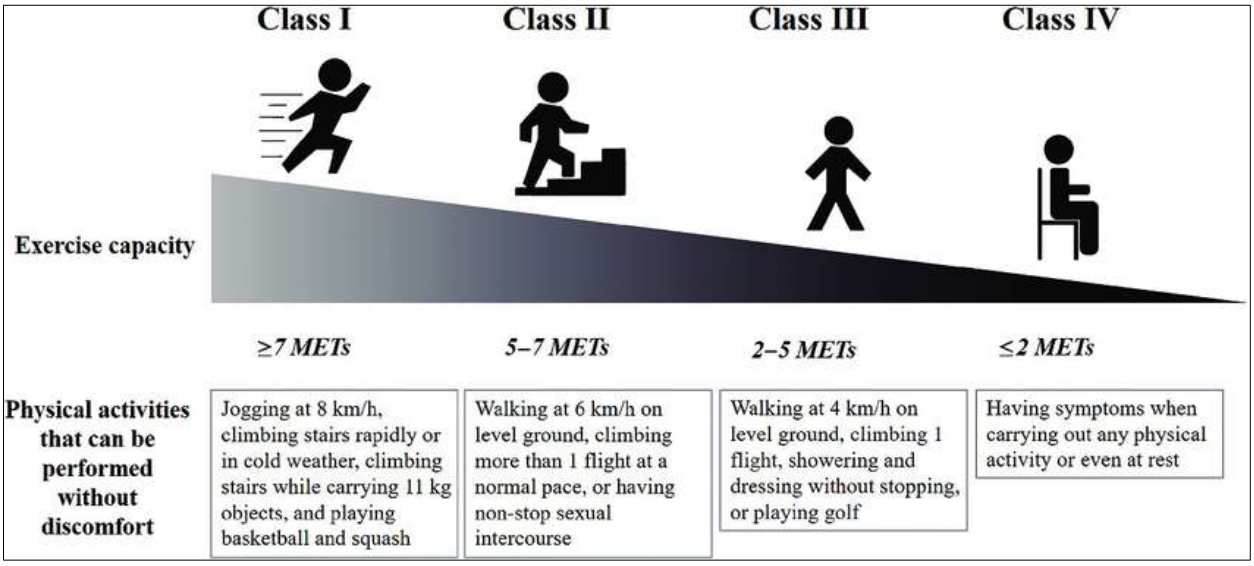

Figure 5: The NYHA classification system and its clinical correlation with patient functional capacity

3.5 ACC/AHA Staging System

The NYHA classification system exists alongside the American College of Cardiology/American Heart Association (ACC/AHA) staging system which shows the progressive development of heart failure (Figure 6). The model consists of four stages which begin with Stage A for people who have high risk of heart failure development without structural heart disease (e.g., hypertension or diabetes) and progress to Stage B for those with structural heart disease (e.g. post-myocardial infarction) without symptoms. Stage C describes patients who have structural heart disease and either current or past heart failure symptoms while Stage D describes patients who need specialized care through mechanical circulatory support or transplant evaluation [26].

The ACC/AHA stages differ from NYHA because patients cannot move backward to lower stages after advancing to higher stages. The model places strong emphasis on early detection and prevention especially for patients at Stage A or B and establishes a complete approach for extended care [27].

NYHA classification		ACC/AHA classification	
Description	Class	Class	Description
	—	A	High risk of developing heart failure but no functional or structural heart deficits
No limitation and no symptoms from ordinary activity	I	B	Structural heart deficit but no symptoms
Mild limitation with activity and comfortable at rest or with mild exertion	II	C	Heart failure symptoms due to underlying structural heart deficit with medical management
Significant limitation with any activity and comfortable only at rest	III	C	Heart failure symptoms due to underlying structural heart deficit with medical management
Discomfort with any physical activity and symptoms occurring at rest	IV	D	Advanced disease requiring hospitalization, transplant, or palliative care

Figure 6: Compares the NYHA and ACC/AHA systems, highlighting their distinct yet complementary roles in classifying heart failure

4. Pathophysiological Mechanisms

The end stage of congestive heart failure (CHF) results from multiple structural, molecular and systemic changes that impair heart function. The pathophysiology of CHF is multifactorial and involves a complex interplay between hemodynamic dysfunction, cellular remodeling, neurohormonal activation, inflammation, and genetic regulation. These mechanisms are important for identifying therapeutic targets and guiding the development of effective treatment strategies [28].

4.1 Hemodynamic Abnormalities

The development and progression of CHF depends on hemodynamic changes. The cardiac performance in HFrEF and HFpEF is affected by preload and afterload abnormalities (Figure 7). The ventricular filling pressures are elevated because of fluid retention and venous congestion. The left ventricle must overcome increased afterload resistance to eject blood because of systemic hypertension or vascular stiffness. The myocardium experiences mechanical stress because of these changes which results in decreased stroke volume and cardiac output [29].

The heart's ability to contract and expand properly also plays a major role in the worsening of heart function. HFrEF patients experience systolic dysfunction because their ventricles contract poorly while HFpEF patients develop diastolic dysfunction which prevents their hearts from relaxing and filling properly. Both conditions lead to increased heart pressures which cause pulmonary congestion and reduce blood flow to the body [30].

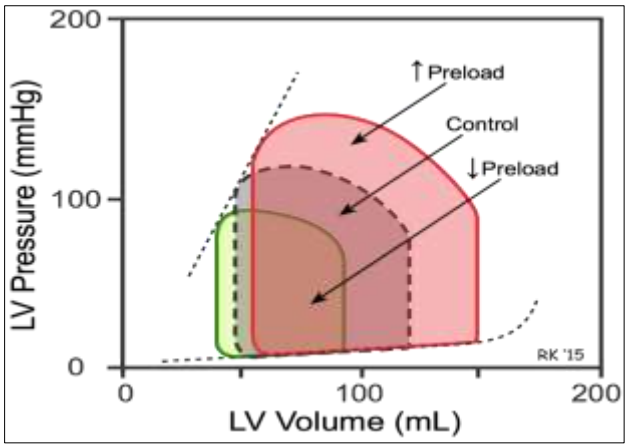

Figure 7: Preload and afterload curves in normal and failing hearts, highlighting the shift in pressure-volume relationships

4.2 Cellular and Molecular Mechanisms

The cellular response to prolonged hemodynamic stress activates multiple harmful processes. The first cellular response to stress is cardiomyocyte hypertrophy (Figure 8) which represents a muscle mass increase to achieve wall stress normalization. The initial protective hypertrophy develops into a pathological condition which damages muscle function and reduces energy efficiency. The process of apoptosis (programmed cell death) occurs simultaneously with this condition which results in permanent damage to functional myocytes [31].

The other characteristic feature includes fibrosis together with extracellular matrix remodeling. The activation of fibroblasts produces excessive collagen which causes myocardial stiffness and disrupts electrical conduction and impairs

diastolic filling. The fibrotic remodeling process stands as the primary factor responsible for HFpEF development. The handling of intracellular calcium shows well-documented abnormalities which are essential for excitation-contraction coupling in CHF. The dysfunction of calcium channels together with sarcoplasmic reticulum proteins causes delayed relaxation and arrhythmias and decreases contractile force [32, 33].

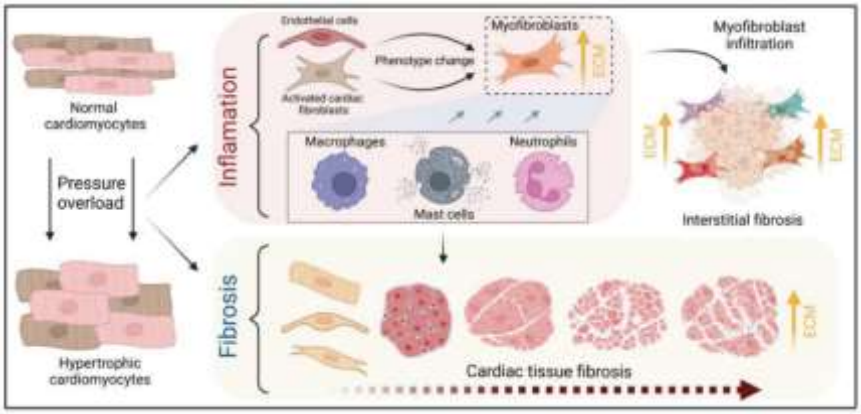

Figure 8: The molecular changes within a cardiomyocyte during hypertrophy

4.3 Neurohormonal Activation

The pathophysiology of CHF includes the persistent activation of neurohormonal systems as its main characteristic. The body uses these responses to preserve blood flow at first but their prolonged activation leads to harmful consequences. The sympathetic nervous system (SNS) represents one of the first neurohormonal systems to become elevated. The sympathetic nervous system activation results in heart rate elevation and muscle contraction force increase while simultaneously causing blood vessel constriction and heart rhythm disturbances and increased myocardial oxygen consumption. The prolonged activation of sympathetic nerves causes damage to heart tissue which leads to worsening heart failure [34].

The renin-angiotensin-aldosterone system (RAAS) activation occurs simultaneously with the sympathetic nervous system upregulation to produce sodium retention and vasoconstriction and fibrosis. The hormone aldosterone triggers both collagen formation and structural changes in the ventricles. The neurohormonal systems create a harmful cycle which sustains cardiac dysfunction [35].

Counter-regulatory mechanisms also exist. The heart releases natriuretic peptides (e.g., BNP, ANP) (Figure 9) to respond to myocardial stretch which leads to natriuresis and vasodilation and RAAS inhibition. The effects of these counter-regulatory mechanisms become less effective in CHF patients because their receptors become less responsive or their signaling pathways become impaired. The condition worsens because vasopressin and endothelin-1 systems along with other mechanisms contribute to increased volume and elevated vascular resistance [36, 37].

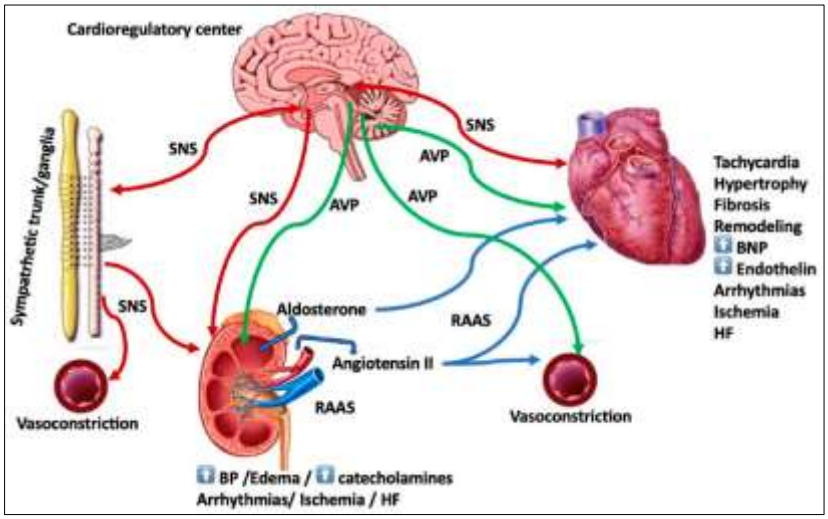

Figure 9: presents a schematic overview of neurohormonal pathways involved in CHF, indicating both detrimental and protective responses

4.4 Inflammation and Oxidative Stress

CHF progresses through inflammation which plays a central role in both non-ischemic and HFpEF forms of the condition (Figure 10). The elevated levels of tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) cytokines in heart failure led to endothelial dysfunction and myocardial apoptosis and catabolic processes. The cytokines enhance tissue remodeling while damaging myocardial function and triggering skeletal muscle atrophy [38].

The excessive generation of reactive oxygen species (ROS) leads to oxidative stress which directly damages lipids proteins and DNA structures in cardiac cells. The failing myocardium experiences worsened energy deficits because mitochondrial dysfunction produces ROS which leads to impaired ATP production. The continuous process of oxidative damage together with inflammation creates ongoing cardiac damage and systemic health problems [39].

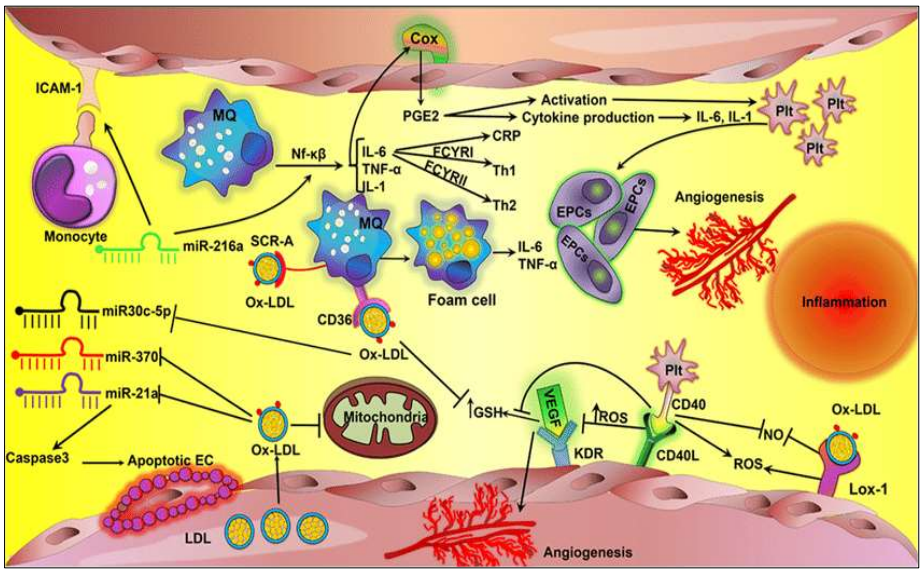

Figure 10: The inflammatory signaling cascades and oxidative stress pathways in CHF, highlighting the interaction between ROS and cytokines

4.5 Genetic and Epigenetic Factors

Genetic predisposition significantly affects CHF development especially when it occurs in familial and idiopathic cardiomyopathies. Mutations in genes that encode sarcomeric proteins (e.g., MYH7, TNNT2) or cytoskeletal elements can cause dilated or hypertrophic cardiomyopathy which develops into heart failure. The inherited forms of these conditions tend to appear at younger ages and need genetic counseling together with specific treatment approaches [40].

Research has shown that epigenetic mechanisms including DNA methylation and histone modification and microRNAs (miRNAs) function as essential regulators of gene expression during heart failure. Specific miRNAs play a role in controlling hypertrophy and fibrosis and apoptosis processes. The modifications can be affected by environmental factors which makes epigenetics a promising therapeutic approach for the future [41].

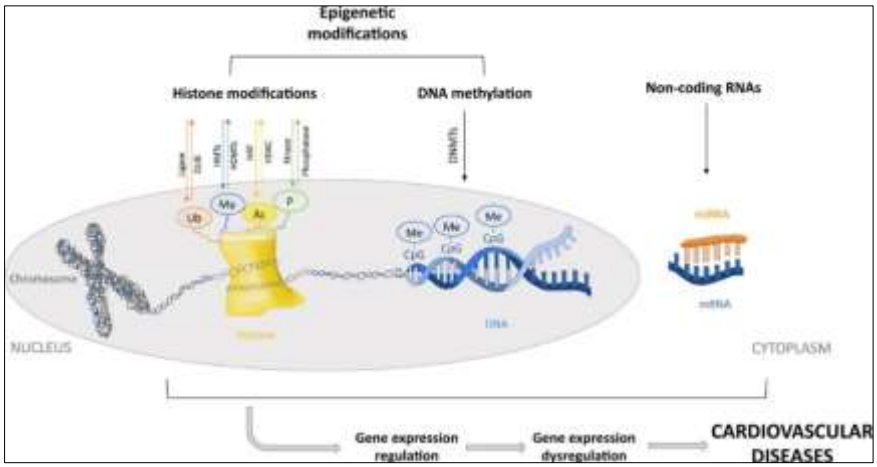

Figure 11: Genetic and epigenetic contributions to CHF, including mutations and regulatory RNA elements

5. Structural and Functional Cardiac Changes

The pathophysiology and clinical presentation of congestive heart failure (CHF) depends on structural and functional heart changes. The myocardial damage from the initial insult leads to active disease progression through these modifications. The combination of cardiac chamber remodeling with valve dysfunction and impaired contraction synchronization leads to decreased cardiac output and increased symptom burden throughout time [42].

5.1 Left Ventricular Remodeling

The left ventricle undergoes remodeling through changes in size and shape and functional alterations when it faces injury or chronic stress. The left ventricle undergoes dilation and wall thinning in HFrEF patients which transforms its shape from elliptical to spherical [43]. The altered ventricular shape decreases mechanical performance while raising wall tension which worsens contractile function. The ventricular wall thickens through concentric hypertrophy in HFpEF patients which reduces chamber volume and impairs both diastolic filling and relaxation [44].

The structural changes result from molecular and cellular mechanisms including cardiomyocyte hypertrophy together with apoptosis and interstitial fibrosis as explained earlier. The process of LV remodeling stands as a major indicator of negative outcomes in CHF patients and represents an essential therapeutic goal. The combination of ACE inhibitors with ARBs and beta-blockers and mineralocorticoid receptor antagonists has proven effective in stopping or slowing down remodeling processes [45].

5.2 Atrial Enlargement

The left atrium shows the most common structural enlargement among CHF patients particularly those with HFpEF. The left atrium experiences dilation because elevated LV filling pressures persistently push back into this chamber leading to atrial stretch and enlargement. The enlargement of atria leads to higher risks of atrial fibrillation which reduces cardiac output and worsens heart failure symptoms [46].

The right atrium can become enlarged because of right-sided heart failure or pulmonary hypertension. The process of atrial remodeling creates electrical conduction problems that lead to higher chances of arrhythmias. The enlarged atria demonstrate decreased contractility which results in reduced ventricular filling capacity and higher probabilities of thromboembolic complications when atrial fibrillation exists [47].

5.3 Valve Dysfunction

The development of CHF leads to valvular heart disease which also serves as a contributing factor to this condition. The heart experiences secondary (functional) mitral and tricuspid regurgitation when volume and pressure overload cause valve leaflets to fail coaptation because of annular dilation or ventricular distortion despite normal leaflet structure. The condition of functional mitral regurgitation occurs frequently in HFrEF because left ventricular dilation causes the mitral apparatus to separate. The regurgitation creates elevated atrial and pulmonary pressures which worsens symptoms of congestion [48].

The initiation of heart failure occurs through primary (organic) valvular lesions which either increase afterload or block forward flow (Figure 12). The dysfunction of valves disrupts typical blood flow patterns which results in myocardial remodeling. Patients who experience persistent symptoms after receiving optimal medical therapy should consider surgical or transcatheter valve repair or replacement [49].

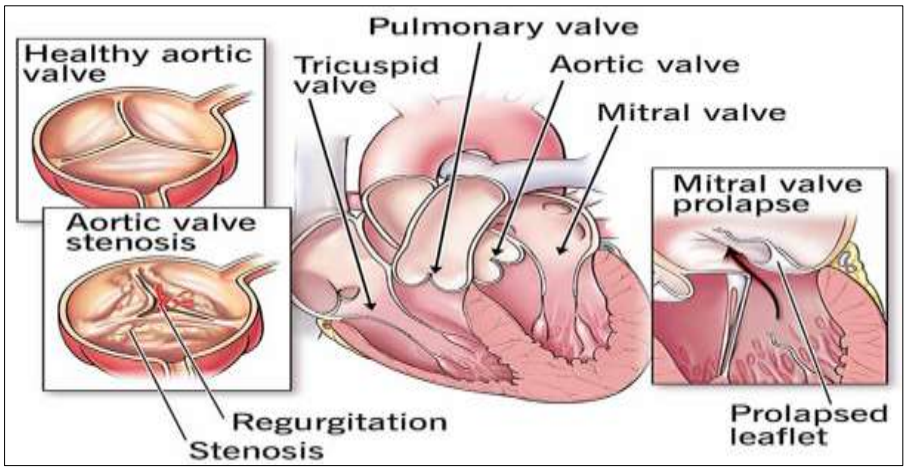

Figure 12: Valvular dysfunction in CHF

5.4 Ventricular Dyssynchrony

The ventricular myocardium shows asynchronous contractions between different regions because of conduction system abnormalities which produce left bundle branch block (LBBB). The inefficient ventricular contraction pattern from dyssynchrony results in decreased stroke volume and worsens mitral regurgitation because of delayed papillary muscle activation. The condition appears most frequently in patients with HFrEF who display wide QRS complexes on electrocardiograms with durations exceeding 120 ms [50].

Cardiac resynchronization therapy (CRT) with biventricular pacing serves as an effective treatment for patients who have dyssynchrony by enhancing both functional status and quality of life and survival rates. The coordinated contraction achieved by CRT improves cardiac efficiency while simultaneously decreasing mitral regurgitation. The identification of dyssynchrony has evolved into a fundamental element for determining heart failure severity and device treatment qualifications [51].

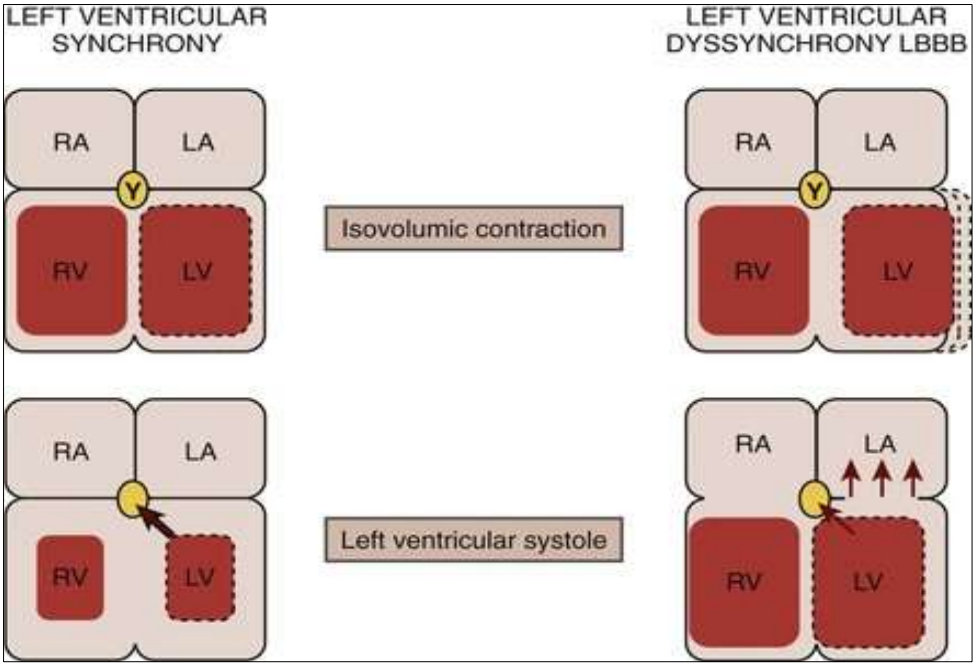

Figure 13: Compares synchronous vs. dyssynchronous ventricular contraction patterns, with QRS duration and mechanical effects

6. Systemic Effects and Multiorgan Involvement

Heart failure exists beyond myocardial disease because it creates a systemic syndrome which impacts various organ systems through hemodynamic compromise and neurohormonal activation and inflammation and metabolic dysregulation. The multiple organ involvement in heart failure leads to major increases in both morbidity and mortality thus requiring complete management of these systemic effects [52].

6.1 Renal Dysfunction (Cardiorenal Syndrome)

The most important systemic effect of heart failure on the body is renal impairment which is known as cardiorenal syndrome (CRS) (Figure 14). The condition is a result of the two-way relationship between the heart and the kidneys where problems in one organ cause or make the other organ's problems worse. The reduced cardiac output in CHF causes renal hypoperfusion which activates the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system in a maladaptive attempt to restore perfusion [53].

The neurohormonal activation causes sodium and water retention which results in volume overload and worsening heart failure and the elevated venous pressures reduce glomerular filtration. The chronic inflammation and oxidative stress in CHF also play a role in the development of renal microvascular dysfunction and fibrosis [54].

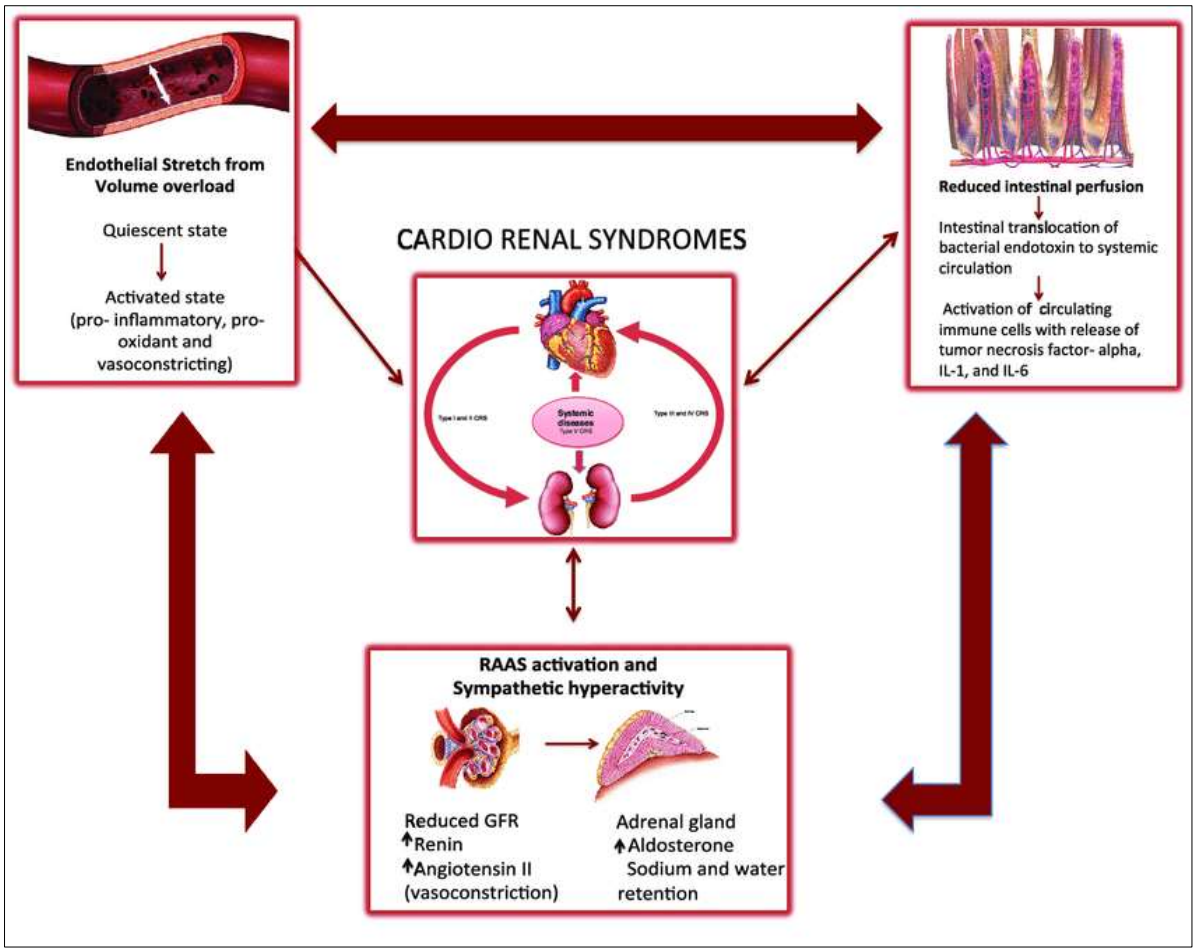

Figure 14: Pathophysiological cycle of cardiorenal syndrome, showing interactions between perfusion pressure, RAAS activation, and tubular damage

6.2 Pulmonary Congestion and Hypertension

The clinical presentation of CHF frequently shows pulmonary complications as its main symptoms. The backward transmission of elevated left-sided filling pressures from HFrEF and HFpEF into the pulmonary circulation results in pulmonary venous congestion. The clinical presentation of dyspnea and orthopnea and pulmonary rales occurs because fluid transudates into alveoli [55]. The prolonged exposure to elevated pressures results in pulmonary hypertension through vasoconstriction and vascular remodeling which eventually causes right ventricular dysfunction. The progression of RV failure creates additional systemic congestion that results in peripheral edema and hepatomegaly and jugular venous distension. Right ventricular failure caused by pulmonary hypertension creates treatment difficulties while leading to poor patient outcomes [56].

6.3 Hepatic Congestion (Cardiohepatic Syndrome)

The liver experiences damage in CHF patients especially when right-sided or biventricular heart failure occurs. The rise of central venous pressure causes passive hepatic congestion which results in hepatomegaly and right upper quadrant discomfort and elevated liver enzymes. The condition develops into cardiac cirrhosis also known as congestive hepatopathy which causes liver fibrosis and reduces synthetic liver capabilities [57].

The liver experiences reduced blood flow during cardiac output lows which results in ischemic damage known as ischemic hepatitis or "shock liver" during acute decompensated heart failure episodes. The disease severity of cardiohepatic syndrome makes it harder to treat patients because it damages drug metabolism and elevates the risk of blood clotting problems [58].

6.4 Skeletal Muscle Wasting and Cachexia

The main systemic expression of CHF appears as skeletal muscle wasting (Figure 15) together with cardiac cachexia which represents a condition of unintentional weight loss and anorexia and muscle atrophy. The condition develops from decreased cardiac output together with chronic inflammation and neurohormonal imbalance and impaired anabolic signaling pathways [59].

The condition of cachexia damages both skeletal and respiratory muscles which results in reduced exercise ability and fatigue and diminished life quality. The combination of elevated catabolic cytokines (e.g., TNF-α, IL-1β) with oxidative stress and impaired mitochondrial function leads to muscle protein breakdown and muscle wasting. The presence of cardiac cachexia leads to elevated death rates and it shows resistance to standard heart failure treatment approaches [60].

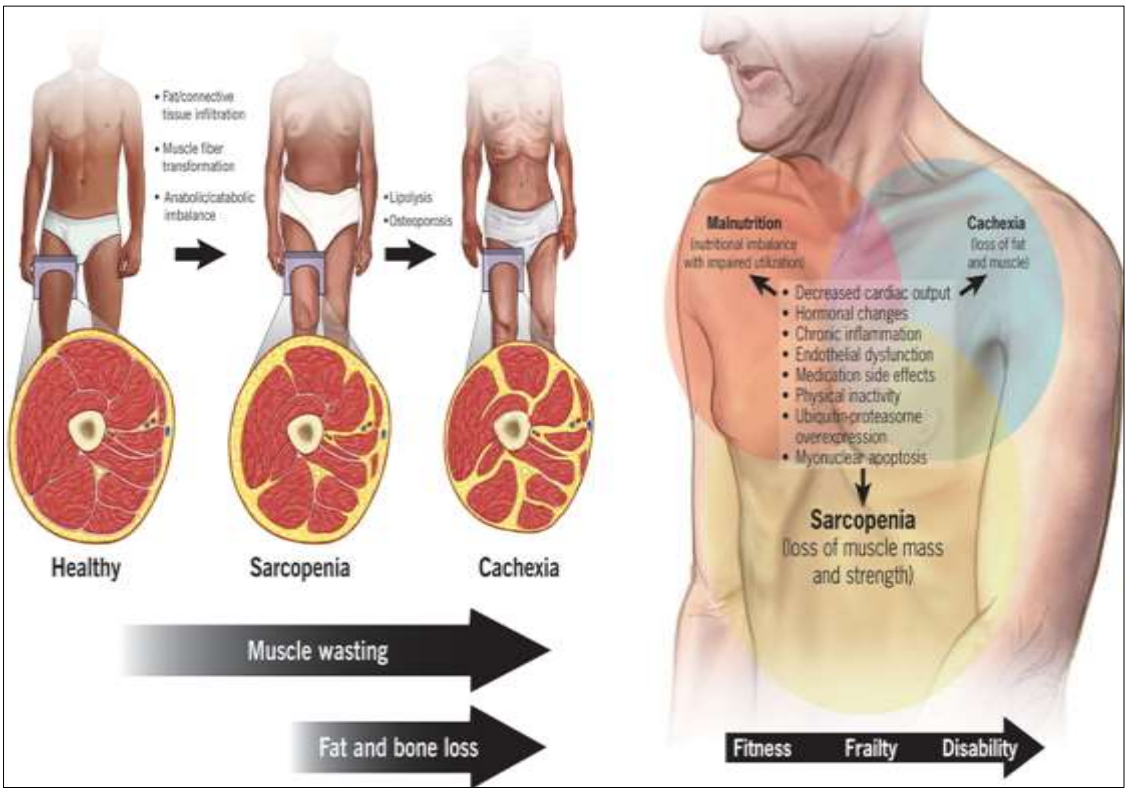

Figure 15: The mechanisms behind muscle wasting in CHF

7. Diagnostic Approach

The diagnosis of congestive heart failure (CHF) needs a complete clinical evaluation which combines history, physical examination, biomarkers, and imaging studies. The correct and prompt diagnosis enables healthcare providers to start proper treatment which leads to better patient results. The diagnostic process for CHF consists of the following essential components [61].

7.1 Clinical Signs and Symptoms

The clinical presentation of CHF shows diversity because it depends on the pathophysiological processes and disease progression stage. The main symptoms of CHF include dyspnea which worsens during exertion or when lying flat (orthopnea) and fatigue together with peripheral edema. The symptoms of patients include both paroxysmal nocturnal dyspnea and decreased exercise capacity. The diagnosis can be supported by physical examination findings that include elevated jugular venous pressure and pulmonary crackles and displaced apical impulse and peripheral edema [62].

The diagnosis of CHF requires more than clinical signs because early and mild cases can be difficult to diagnose through clinical means alone. The interpretation of clinical signs requires consideration of patient history together with comorbidities and risk factors. The diagnosis of HFpEF becomes more challenging because its symptoms often blend with other medical conditions thus requiring additional diagnostic procedures (Figure 16) [63].

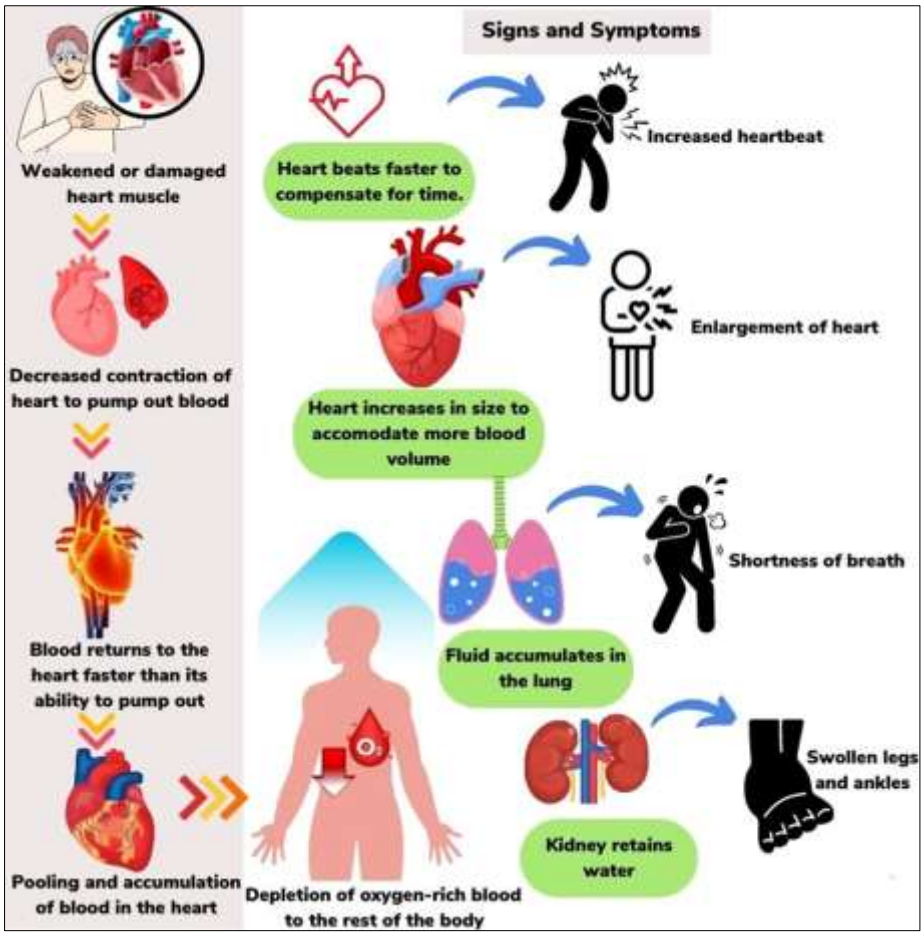

Figure 16: Clinical features of CHF

7.2 Laboratory Markers

Laboratory biomarkers serve as essential tools for CHF diagnosis and severity assessment and prognosis prediction. The B-type natriuretic peptide (BNP) together with its inactive fragment NT-proBNP serve as the primary biomarkers used in clinical practice. The heart muscle cells of the ventricle produce these markers when the heart experiences excessive wall tension and increased volume overload. The test shows high sensitivity and negative predictive value for heart failure which helps doctors identify cardiac causes of dyspnea over non-cardiac causes [64].

The presence of cardiac troponins indicates myocardial injury because these markers appear in the blood when cardiomyocytes experience stress and necrosis in chronic heart failure. The presence of these markers indicates poor prognosis and shows evidence of either ischemic or non-ischemic myocardial damage. The evaluation of comorbidities and potential reversible causes of CHF requires essential laboratory tests including renal and liver function tests as well as electrolytes and thyroid function tests [65].

7.3 Imaging

The diagnosis confirmation and cardiac structure evaluation and function assessment and etiology detection heavily rely on imaging modalities. Echocardiography stands as the primary imaging tool because it provides immediate assessment of ventricular size and ejection fraction and wall motion abnormalities and valve function and filling pressure estimation [66].

Cardiac magnetic resonance imaging (MRI) provides better tissue identification and precise measurements of ventricular dimensions and fibrosis. The technique proves most beneficial for complex cases including infiltrative cardiomyopathies and situations where echocardiographic images are not clear. Computed tomography (CT) serves as a less frequent diagnostic tool which helps doctors evaluate coronary artery disease and structural anomalies [67].

7.4 Hemodynamic Assessment

Right heart catheterization serves as the only method to measure intracardiac pressures and cardiac output and vascular resistance in specific clinical situations. The procedure becomes essential when doctors need to determine the

cause of diagnostic uncertainty or when patients show severe symptoms that do not respond to treatment or when they need mechanical circulatory support or transplantation [68].

The assessment of hemodynamic data enables healthcare providers to identify heart failure types and evaluate pulmonary hypertension while creating individualized treatment plans. Doppler echocardiography provides non-invasive estimates of certain hemodynamic parameters although direct measurement remains more accurate [69].

8. Current Therapeutic Strategies

The management of congestive heart failure (CHF) needs a combination of pharmacologic treatments, lifestyle modifications, device therapies, and surgical interventions. The main objectives are to reduce symptoms, enhance quality of life, decrease hospital admissions, and increase survival. The treatment plan is usually individualized according to the type of heart failure, the cause of the heart failure, and the patient's characteristics [70].

8.1 Pharmacologic Therapies

Pharmacotherapy stands as the fundamental treatment for CHF management because different drug classes provide mortality and morbidity benefits particularly for patients with heart failure with reduced ejection fraction (HFrEF) [71].

The renin-angiotensin-aldosterone system (RAAS) pathway which causes maladaptive remodeling and fluid retention is targeted by Angiotensin-Converting Enzyme (ACE) Inhibitors Angiotensin Receptor Blockers (ARBs) and Angiotensin Receptor-Neprilysin Inhibitors (ARNIs) [72]. ACE inhibitors lower blood pressure and stop ventricular remodeling which results in better survival rates and improved symptoms for patients. Patients who cannot take ACE inhibitors can use ARBs as an alternative treatment while sacubitril/valsartan represents an ARNI that combines RAAS blockade with natriuretic peptide enhancement to deliver better outcomes [73, 74].

Beta-blockers reduce excessive sympathetic nervous system activity which leads to decreased heart rate and myocardial oxygen consumption and reduced risk of arrhythmias. These agents have shown significant mortality reduction and are indicated in all stable patients with HFrEF [75].

The mineralocorticoid receptor-blocking agents spironolactone and eplerenone reduce sodium retention and fibrosis while providing additional benefits for survival and hospitalization prevention. Diuretics play a crucial role in fluid overload management for symptomatic relief but they do not impact long-term survival rates [76].

The Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors which started as diabetes treatments now prove effective in CHF management by reducing hospitalizations and cardiovascular deaths in both diabetic and non-diabetic patients through natriuresis and improved myocardial metabolism and reduced inflammation [77].

8.2 Non-Pharmacologic Interventions

The management of CHF depends heavily on lifestyle changes. Patients need to follow sodium and fluid limits while keeping their weight at a healthy level and doing physical activities according to their tolerance [78].

Cardiac rehabilitation programs offer supervised exercise training together with education and psychosocial support which enhances functional capacity and symptom control and quality of life. These programs deliver the most benefit to patients after acute decompensation or cardiac procedures [79].

8.3 Device-Based Therapies

The device therapies show improved outcomes for selected patients who have advanced CHF together with particular electrical conduction abnormalities. The implantable cardioverter-defibrillators (ICDs) function to detect dangerous arrhythmias which then get terminated to prevent sudden cardiac death [80].

The biventricular pacing method of cardiac resynchronization therapy (CRT) corrects ventricular dyssynchrony to enhance cardiac efficiency and reverse remodeling and improve symptoms and survival rates in patients with wide QRS complexes. Left ventricular assist devices (LVADs) provide mechanical circulatory support to patients with end-stage heart failure who do not respond to medical and device therapy through either bridge-to-transplantation or destination therapy [81].

8.4 Surgical Options

Heart transplantation serves as the only definitive treatment for specific patients with end-stage heart failure because it provides substantial survival advantages and better quality of life. The scarcity of donor organs together with post-transplant complications restricts the use of this treatment [82]. Surgical procedures that repair or replace valves treat

both valvular origins and valvular effects of CHF particularly when medical management fails to address severe regurgitation or stenosis. The development of minimally invasive and transcatheter techniques has created new treatment possibilities for patients who face high risks [83].

9. Emerging Therapies and Future Directions

Standard treatments have not eliminated congestive heart failure (CHF) from being a major global health challenge. Research continues to focus on discovering new therapeutic targets while implementing advanced technologies and tailoring treatments to enhance patient results. This section examines new therapeutic approaches and future directions for CHF management [84].

9.1 Novel Pharmacological Targets

The recent discoveries in molecular biology and pathophysiology have revealed new pharmacological targets which extend past the traditional neurohormonal pathways. Researchers are studying drugs that target inflammation pathways and fibrosis and metabolic regulation. The development of TGF-β and galectin-3 inhibitors represents a promising approach to minimize adverse cardiac remodeling [85].

The development of omecamtiv mecarbil as a myosin activator represents one of several promising drugs which enhance myocardial contractility without raising oxygen consumption and drugs that target mitochondrial dysfunction and oxidative stress. Research continues on drugs that affect the sodium-hydrogen exchanger and serelaxin (human relaxin-2 recombinant form) because they show potential to enhance cardiac and systemic vascular function [86].

9.2 Gene and Cell Therapy

Gene therapy creates a new therapeutic approach that directly addresses heart failure through genetic and molecular interventions. The delivery of genes that produce proteins which enhance contractility and calcium handling and angiogenesis forms part of these techniques. The introduction of therapeutic genes into cardiomyocytes through viral vectors in early-phase clinical trials demonstrates potential for myocardial function recovery [87].

Stem cells and progenitor cells used in cell therapy work to rebuild damaged heart tissue while creating new blood vessels and controlling inflammation. The results have been inconsistent but researchers predict that improved cell selection techniques and delivery methods and genetic engineering advancements will lead to better outcomes. Future research indicates that combining gene and cell therapies could produce enhanced therapeutic effects [88].

9.3 Precision Medicine Approaches

The diverse nature of CHF requires healthcare providers to develop individualized treatment plans. Precision medicine uses genetic and proteomic and metabolomic and phenotypic information to create personalized treatment plans for each patient. The method allows healthcare providers to detect particular disease processes and individual response indicators and risk assessment patterns [89].

Through pharmacogenomics healthcare providers can determine which patients will gain benefits from medications and which patients will experience adverse effects thus enabling better drug selection and dosing. The combination of multi-omics data with clinical variables enables better risk assessment and earlier treatment initiation which could shift CHF care from standard treatment to personalized precision medicine [90].

9.4 Role of Artificial Intelligence in Diagnosis and Management

The healthcare of congestive heart failure (CHF) receives transformation through artificial intelligence (AI) and machine learning technologies which improve diagnostic precision and risk assessment and treatment customization. AI algorithms process extensive health record data alongside imaging results and wearable sensor information to detect early heart failure signs and impending decompensation indicators [91].

Predictive models help medical professionals make better decisions while optimizing therapy modifications and reducing hospitalization rates. AI-powered imaging analysis enhances echocardiogram and cardiac MRI interpretation through reduced inter-observer variability. The implementation of AI technology in telemedicine systems enables remote patient monitoring which leads to better healthcare results and system efficiency [92].

10. Clinical Implications and Practice Integration

The deep understanding of congestive heart failure (CHF) pathophysiology creates essential implications for medical practice. The application of mechanistic knowledge in patient care enables healthcare providers to diagnose patients more precisely and deliver effective treatments that lead to better prognostic results.

The treatment of CHF requires individualized care because the condition exists in different forms regarding its causes and its severity levels and associated medical conditions. Medical practitioners need to combine clinical observations with laboratory results and imaging findings to create personalized treatment plans that match each patient's pathophysiological condition and individual requirements. The therapeutic approach delivers maximum effectiveness while reducing potential adverse reactions.

The delivery of complete heart failure care depends heavily on multidisciplinary teams consisting of cardiologists and primary care physicians and nurses and pharmacists and dietitians and rehabilitation specialists. The collaborative approach between healthcare providers leads to better medication adherence and lifestyle changes and quicker detection of decompensation and psychosocial support which results in improved outcomes and decreased hospitalizations.

11. CONCLUSION

The review explains the complex pathophysiological mechanisms of congestive heart failure which include hemodynamic abnormalities and cellular and molecular dysfunctions and neurohormonal activation and systemic organ involvement. The knowledge of these processes enables healthcare providers to develop specific diagnostic approaches and treatment plans.

The prevention of permanent cardiac remodeling and systemic complications depends on early intervention. The management of CHF requires a complete approach which combines pharmacologic treatments with device-based interventions and lifestyle modifications to enhance survival rates and improve quality of life.

The field continues to face ongoing challenges because of its diverse nature and treatment challenges and limited resources. Future research should concentrate on precision medicine and emerging therapies and innovative technologies to improve CHF care and patient outcomes.

REFERENCES

1. Yancy, C. W., Jessup, M., Bozkurt, B., *et al*. (2017). 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation, 136*(6), e137–e161. https://doi.org/10.1161/CIR.0000000000000509
2. Lund, L. H., Claggett, B., Liu, J., *et al*. (2018). Heart failure with mid-range ejection fraction in CHARM: Characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. European Journal of Heart Failure, 20(8), 1230–1239. https://doi.org/10.1002/ejhf.1149
3. Virani, S. S., Alonso, A., Aparicio, H. J., *et al*. (2021). Heart disease and stroke statistics—2021 update: A report from the American Heart Association. Circulation, 143(8), e254–e743. https://doi.org/10.1161/CIR.0000000000000950
4. Urbich, M., Globe, G., Pantiri, K., Heisen, M., Bennison, C., Wirtz, H. S., & Di Tanna, G. L. (2020). A systematic review of medical costs associated with heart failure in the USA (2014–2020). Pharmacoeconomics, 38(11), 1219–1236. https://doi.org/10.1007/s40273-020-00952-0
5. Savarese, G., Becher, P. M., Lund, L. H., Seferovic, P., Rosano, G. M. C., & Coats, A. J. S. (2023). Global burden of heart failure: A comprehensive and updated review of epidemiology. Cardiovascular Research, 118(17), 3272–3287. https://doi.org/10.1093/cvr/cvac013
6. King-Dailey, K., Frazier, S., Bressler, S., & King-Wilson, J. (2022). The role of nurse practitioners in the management of heart failure patients and programs. Current Cardiology Reports, 24(12), 1945–1956. https://doi.org/10.1007/s11886-022-01796-0
7. Benjamin, E. J., Muntner, P., Alonso, A., *et al.* (2019). Heart disease and stroke statistics—2019 update: A report from the American Heart Association. Circulation, 139(10), e56–e528. https://doi.org/10.1161/CIR.0000000000000659
8. Dunlay, S. M., Roger, V. L., & Redfield, M. M. (2017). Epidemiology of heart failure with preserved ejection fraction. Nature Reviews Cardiology, 14(10), 591–602. https://doi.org/10.1038/nrcardio.2017.65
9. Lewsey, S. C., & Breathett, K. (2021). Racial and ethnic disparities in heart failure: Current state and future directions. Current Opinion in Cardiology, 36(3), 320–328. https://doi.org/10.1097/HCO.0000000000000855
10. Li, X., Chan, J. S. K., Guan, B., Peng, S., Wu, X., Lu, X., et al. (2022). Triglyceride-glucose index and the risk of heart failure: Evidence from two large cohorts and a Mendelian randomization analysis. Cardiovascular Diabetology, 21, 229. https://doi.org/10.1186/s12933-022-01658-7
11. Abdin, A., Anker, S. D., Butler, J., Coats, A. J. S., Kindermann, I., Lainscak, M., et al. (2021). 'Time is prognosis' in heart failure: Time-to-treatment initiation as a modifiable risk factor. ESC Heart Failure, 8, 4444–4453. https://doi.org/10.1002/ehf2.13646
12. Kamiya, K., Sato, Y., Takahashi, T., Tsuchihashi-Makaya, M., Kotooka, N., Ikegame, T., et al. (2020). Multidisciplinary cardiac rehabilitation and long-term prognosis in patients with heart failure. Circulation: Heart Failure, 13, e006798. https://doi.org/10.1161/CIRCHEARTFAILURE.119.006798

13. Ahmad, M. S., Alharbi, A. O. M., Tawakul, A., Alturiqy, A. M., Alzahrani, M., & Shaik, R. A. (2025). A case-control study on risk factors and outcomes in congestive heart failure. Reviews in Cardiovascular Medicine, 26(3), 26601. https://doi.org/10.31083/RCM26601
14. Nair, N. (2020). Epidemiology and pathogenesis of heart failure with preserved ejection fraction. Reviews in Cardiovascular Medicine, 21, 531–540. https://doi.org/10.31083/j.rcm.2020.04.154
15. Arrigo, M., Jessup, M., Mullens, W., Reza, N., Shah, A. M., Sliwa, K., et al. (2020). Acute heart failure. Nature Reviews Disease Primers, 6, 16. https://doi.org/10.1038/s41572-020-0151-7
16. Pagliaro, B. R., Cannata, F., Stefanini, G. G., & Bolognese, L. (2020). Myocardial ischemia and coronary disease in heart failure. Heart Failure Reviews, 25, 53–65. https://doi.org/10.1007/s10741-019-09831-z
17. Kwok, C. S., Abramov, D., Parwani, P., Ghosh, R. K., Kittleson, M., Ahmad, F. Z., et al. (2021). Cost of inpatient heart failure care and 30-day readmissions in the United States. International Journal of Cardiology, 329, 115–122. https://doi.org/10.1016/j.ijcard.2020.12.020
18. Lewsey, S. C., & Breathett, K. (2021). Racial and ethnic disparities in heart failure: Current state and future directions. Current Opinion in Cardiology, 36(3), 320–328. https://doi.org/10.1097/HCO.0000000000000855
19. Pandey, A., Khan, M. S., Patel, K. V., Bhatt, D. L., & Verma, S. (2023). Predicting and preventing heart failure in type 2 diabetes. The Lancet Diabetes & Endocrinology, 11, 607–624. https://doi.org/10.1016/S2213-8587(23)00128-6
20. Roger, V. L. (2021). Epidemiology of heart failure: A contemporary perspective. Circulation Research, 128, 1421–1434. https://doi.org/10.1161/CIRCRESAHA.121.318172
21. Sinnenberg, L., & Givertz, M. M. (2020). Acute heart failure. Trends in Cardiovascular Medicine, 30, 104–112. https://doi.org/10.1016/j.tcm.2019.03.007
22. Triposkiadis, F., Xanthopoulos, A., Parissis, J., Butler, J., & Farmakis, D. (2022). Pathogenesis of chronic heart failure: Cardiovascular aging, risk factors, comorbidities, and disease modifiers. Heart Failure Reviews, 27, 337–344. https://doi.org/10.1007/s10741-020-09987-z
23. Nair, A., Tuan, L. Q., Jones-Lewis, N., Raja, D. C., Shroff, J., & Pathak, R. K. (2024). Heart failure with mildly reduced ejection fraction—A phenotype waiting to be explored. Journal of Cardiovascular Development and Disease, 11(5), 148. https://doi.org/10.3390/jcdd11050148
24. Docherty, K. F., Bayes-Genis, A., Butler, J., Coats, A. J. S., Drazner, M. H., Joyce, E., & Lam, C. S. P. (2022). The four pillars of HFrEF therapy: Is it time to treat heart failure regardless of ejection fraction? European Heart Journal Supplements, 24(Suppl L), L10–L19. https://doi.org/10.1093/eurheartjsupp/suac113
25. Raphael, C., Briscoe, C., Davies, J., Whinnett, Z. I., Manisty, C., Sutton, R., Mayet, J., & Francis, D. P. (2007). Limitations of the New York Heart Association functional classification system and self-reported walking distances in chronic heart failure. Heart, 93(4), 476–482. https://doi.org/10.1136/hrt.2006.089656
26. Golla, M. S. G., & Shams, P. (2024). Heart failure with preserved ejection fraction (HFpEF). In StatPearls. StatPearls Publishing. Retrieved June 8, 2025, from https://www.ncbi.nlm.nih.gov/books/NBK599960/
27. Bozkurt, B., Coats, A. J. S., Tsutsui, H. *et al*. (2021). Universal definition and classification of heart failure: A report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. *European Journal of Heart Failure*. Advance online publication. https://doi.org/10.1002/ejhf.2115
28. Hsu, S., Fang, J. C., & Borlaug, B. A. (2022). Hemodynamics for the heart failure clinician: A state-of-the-art review. Journal of Cardiac Failure, 28(1), 133–148. https://doi.org/10.1016/j.cardfail.2021.07.012
29. Obokata, M., Kane, G. C., Reddy, Y. N. V., Olson, T. P., Melenovsky, V., & Borlaug, B. A. (2017). Role of diastolic stress testing in the evaluation for HFpEF: A simultaneous invasive-echocardiographic study. Circulation, 135(9), 825–838. https://doi.org/10.1161/CIRCULATIONAHA.116.024822
30. Borlaug, B. A., & Kass, D. A. (2009). Invasive hemodynamic assessment in heart failure. Heart Failure Clinics, 5(2), 217–228. https://doi.org/10.1016/j.hfc.2008.11.008
31. Schwartzenberg, S., Redfield, M. M., From, A. M., Sorajja, P., Nishimura, R. A., & Borlaug, B. A. (2012). Effects of vasodilation in pulmonary hypertension with preserved or reduced ejection fraction. Journal of the American College of Cardiology, 59(5), 442–451. https://doi.org/10.1016/j.jacc.2011.09.062
32. Burkhoff, D., Sayer, G., Doshi, D., & Uriel, N. (2015). Hemodynamics of mechanical circulatory support. Journal of the American College of Cardiology, 66(23), 2663–2674. https://doi.org/10.1016/j.jacc.2015.10.017
33. Hsu, S., Kambhampati, S., Sciortino, C. M., Russell, S. D., & Schulman, S. P. (2018). Predictors of intra-aortic balloon pump hemodynamic failure in non-acute myocardial infarction cardiogenic shock. American Heart Journal, 199, 181–191. https://doi.org/10.1016/j.ahj.2017.11.016
34. Borlaug, B. A., Lam, C. S. P., Roger, V. L., Rodeheffer, R. J., & Redfield, M. M. (2009). Contractility and ventricular systolic stiffening in hypertensive heart disease: Insights into the pathogenesis of HFpEF. Journal of the American College of Cardiology, 54(5), 410–418. https://doi.org/10.1016/j.jacc.2009.05.013
35. Hammo, Z. S. Y., Almahdawi, Z. M., Abbas, S. K., & Tahir, N. T. (2023). The role of homocysteine and MCP-1 levels in patients with angina pectoris or congestive heart failure. Journal of Cardiovascular Disease Research, 14(1), 2945–2963. https://doi.org/10.31838/jc9r.2022.13.08.381

36. Mustafa, A. A., Hammo, Z. S. Y., & Tuama, R. M. (2025). A review on brain-heart axis physiology and its clinical implications. International Journal of Medicine Sciences, 7(1), 41–51. https://doi.org/10.33545/26648881.2025.v7.i1a.59
37. Kawaguchi, M., Hay, I., Fetics, B., & Kass, D. A. (2003). Combined ventricular systolic and arterial stiffening in patients with HFpEF: Implications for systolic and diastolic reserve limitations. Circulation, 107(5), 714–720. https://doi.org/10.1161/01.cir.0000048123.22359.a0
38. Vonk Noordegraaf, A., Chin, K. M., Haddad, F., et al. (2019). Pathophysiology of the right ventricle and of the pulmonary circulation in pulmonary hypertension: An update. European Respiratory Journal, 53(1), 1801900. https://doi.org/10.1183/13993003.01900-2018
39. Borlaug, B. A., Kane, G. C., Melenovsky, V., & Olson, T. P. (2016). Abnormal right ventricular-pulmonary artery coupling with exercise in HFpEF. European Heart Journal, 37(43), 3293–3302. https://doi.org/10.1093/eurheartj/ehw241
40. Sajeev, C. G., Nair, S., George, B., & Krishnan, M. N. (2016). Demographical and clinicopathological characteristics in heart failure and outcome predictors: A prospective, observational study. ESC Heart Failure, 4(1). https://doi.org/10.1002/ehf2.12119
41. Chulenbayeva, L., Issilbayeva, A., Sailybayeva, A., Bekbossynova, M., Kozhakhmetov, S., & Kushugulova, A. (2025). Short-Chain Fatty Acids and Their Metabolic Interactions in Heart Failure. Biomedicines, 13(2), 343. https://doi.org/10.3390/biomedicines13020343
42. Cvijic, M., Rib, Y., Danojevic, S., et al. (2023). Heart failure with mildly reduced ejection fraction: From diagnosis to treatment. Gaps and dilemmas in current clinical practice. Heart Failure Reviews, 28, 767–780. https://doi.org/10.1007/s10741-022-10267-1
43. Schwinger, R. H. G. (2021). Pathophysiology of heart failure. *Cardiovascular Diagnosis and Therapy, 11*(1), 263–276. https://doi.org/10.21037/cdt-20-302
44. Ponikowski, P., Voors, A. A., Anker, S. D., et al. (2016). 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *European Heart Journal, 37*(27), 2129–2200. https://doi.org/10.1093/eurheartj/ehw128
45. Tanai, E., & Frantz, S. (2015). Pathophysiology of heart failure. *Comprehensive Physiology, 6*(1), 187–214. https://doi.org/10.1002/cphy.c140055
46. Boekel, N. B., Duane, F. K., Jacobse, J. N., et al. (2020). Heart failure after treatment for breast cancer. *European Journal of Heart Failure, 22*(3), 366–374. https://doi.org/10.1002/ejhf.1620
47. Cardinale, D., Colombo, A., Bacchiani, G., et al. (2015). Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. *Circulation, 131*(22), 1981–1988. https://doi.org/10.1161/CIRCULATIONAHA.114.013777
48. Groarke, J. D., & Nohria, A. (2015). Anthracycline cardiotoxicity: A new paradigm for an old classic. *Circulation, 131*(21), 1946–1949. https://doi.org/10.1161/CIRCULATIONAHA.115.016704
49. Lane, R. E., Cowie, M. R., & Chow, A. W. (2005). Prediction and prevention of sudden cardiac death in heart failure. *Heart, 91*(6), 674–680. https://doi.org/10.1136/hrt.2003.025254
50. Simmonds, S. J., Cuijpers, I., Heymans, S., et al. (2020). Cellular and molecular differences between HFpEF and HFrEF: A step ahead in an improved pathological understanding. *Cells, 9*(1), 242. https://doi.org/10.3390/cells9010242
51. Lee, D. S., Gona, P., Vasan, R. S., et al. (2009). Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: Insights from the Framingham Heart Study of the National Heart, Lung, and Blood Institute. *Circulation, 119*(23), 3070–3077. https://doi.org/10.1161/CIRCULATIONAHA.108.815944
52. He, J., Ogden, L. G., Bazzano, L. A., et al. (2001). Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. *Archives of Internal Medicine, 161*(7), 996–1002. https://doi.org/10.1001/archinte.161.7.996
53. Borlaug, B. A., Melenovsky, V., Russell, S. D., et al. (2006). Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. *Circulation, 114*(21), 2138–2147. https://doi.org/10.1161/CIRCULATIONAHA.106.632745
54. van Heerebeek, L., Borbely, A., Niessen, H. W., et al. (2006). Myocardial structure and function differ in systolic and diastolic heart failure. *Circulation, 113*(16), 1966–1973. https://doi.org/10.1161/CIRCULATIONAHA.105.587519
55. Czepluch, F. S., Wollnik, B., & Hasenfuß, G. (2018). Genetic determinants of heart failure: Facts and numbers. *ESC Heart Failure, 5*(2), 211–217. https://doi.org/10.1002/ehf2.12267
56. Anand, I., McMurray, J. J., Whitmore, J., et al. (2004). Anemia and its relationship to clinical outcome in heart failure. *Circulation, 110*(2), 149–154. https://doi.org/10.1161/01.CIR.0000134279.79571.73
57. Anand, I. S., & Gupta, P. (2018). Anemia and iron deficiency in heart failure. *Circulation, 138*(1), 80–98. https://doi.org/10.1161/CIRCULATIONAHA.118.030099
58. Anker, S. D., Comin Colet, J., Filippatos, G., et al. (2009). Ferric carboxymaltose in patients with heart failure and iron deficiency. *New England Journal of Medicine, 361*(25), 2436–2448. https://doi.org/10.1056/NEJMoa0908355

59. Damman, K., Valente, M. A. E., Voors, A. A., et al. (2014). Renal impairment, worsening renal function, and outcome in patients with heart failure: An updated meta-analysis. *European Heart Journal, 35*(7), 455–469. https://doi.org/10.1093/eurheartj/eht386
60. Gilbert, R. E., & Krum, H. (2015). Heart failure in diabetes: Effects of anti-hyperglycaemic drug therapy. *Lancet, 385*(9982), 2107–2117. https://doi.org/10.1016/S0140-6736(14)61402-1
61. Boussageon, R., Supper, I., Bejan-Angoulvant, T., et al. (2012). Reappraisal of metformin efficacy in the treatment of type 2 diabetes: A meta-analysis of randomised controlled trials. *PLoS Medicine, 9*(4), e1001204. https://doi.org/10.1371/journal.pmed.1001204
62. Verma, S., & McMurray, J. J. V. (2018). SGLT2 inhibitors and mechanisms of cardiovascular benefit: A state-of-the-art review. *Diabetologia, 61*(10), 2108–2117. https://doi.org/10.1007/s00125-018-4670-7
63. Gary S. Francis, W.H. Wilson Tang. Pathophysiology of Congestive Heart Failure. Rev. Cardiovasc. Med. 2003, 4(S2), 14–20.
64. Melo, L. G., Veress, A. T., Ackermann, U., & Sonnenberg, H. (1998). Chronic regulation of arterial blood pressure by ANP: Role of endogenous vasoactive endothelial factors. *American Journal of Physiology*, *275*(5), H1826–H1833. https://doi.org/10.1152/ajpheart.1998.275.5.H1826
65. Eiserich, J. P., Hristova, M., Cross, C. E., Jones, A. D., Freeman, B. A., Halliwell, B., et al. (1998). Formation of nitric oxide-derived inflammatory oxidants by myeloperoxidase in neutrophils. *Nature*, *391*(6665), 393–397. https://doi.org/10.1038/34923
66. Liu, V. W., & Huang, P. L. (2008). Cardiovascular roles of nitric oxide: A review of insights from nitric oxide synthase gene disrupted mice. *Cardiovascular Research*, *77*(1), 19–29. https://doi.org/10.1016/j.cardiores.2007.06.024
67. Wilkinson, I. B., Franklin, S. S., & Cockcroft, J. R. (2004). Nitric oxide and the regulation of large artery stiffness: From physiology to pharmacology. *Hypertension*, *44*(1), 112–116. https://doi.org/10.1161/01.HYP.0000138068.03893.40
68. Bhushan, S., Kondo, K., Polhemus, D. J., Otsuka, H., Nicholson, C. K., Tao, Y. X., et al. (2014). Nitrite therapy improves left ventricular function during heart failure via restoration of nitric oxide-mediated cytoprotective signaling. *Circulation Research*, *114*(8), 1281–1291. https://doi.org/10.1161/CIRCRESAHA.114.301475
69. Jackson, G., Gibbs, C. R., Davies, M. K., & Lip, G. Y. (2000). ABC of heart failure. Pathophysiology. *BMJ*, *320*(7228), 167–170. https://doi.org/10.1136/bmj.320.7228.167
70. Weber, K. T. (2001). Aldosterone in congestive heart failure. *The New England Journal of Medicine*, *345*(22), 1689–1697. https://doi.org/10.1056/NEJMra000050
71. von Lueder, T. G., Sangaralingham, S. J., Wang, B. H., Kompa, A. R., Atar, D., Burnett, J. C. Jr., et al. (2013). Renin-angiotensin blockade combined with natriuretic peptide system augmentation: Novel therapeutic concepts to combat heart failure. *Circulation: Heart Failure*, *6*(3), 594–605. https://doi.org/10.1161/CIRCHEARTFAILURE.112.000289
72. Beygui, F., Vicaut, E., Ecollan, P., Machecourt, J., Van Belle, E., Zannad, F., et al. (2010). Rationale for an early aldosterone blockade in acute myocardial infarction and design of the ALBATROSS trial. *American Heart Journal*, *160*(4), 642–648. https://doi.org/10.1016/j.ahj.2010.06.049
73. Pitt, B., Remme, W., Zannad, F., Neaton, J., Martinez, F., Roniker, B., et al. (2003). Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *The New England Journal of Medicine*, *348*(14), 1309–1321. https://doi.org/10.1056/NEJMoa030207
74. Pitt, B., White, H., Nicolau, J., Martinez, F., Gheorghiade, M., Aschermann, M., et al. (2005). Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. *Journal of the American College of Cardiology*, *46*(3), 425–431. https://doi.org/10.1016/j.jacc.2005.04.038
75. Vigliano, C. A., Cabeza Meckert, P. M., Diez, M., Favaloro, L. E., Cortes, C., Fazzi, L., et al. (2011). Cardiomyocyte hypertrophy, oncosis, and autophagic vacuolization predict mortality in idiopathic dilated cardiomyopathy with advanced heart failure. *Journal of the American College of Cardiology*, *57*(13), 1523–1531. https://doi.org/10.1016/j.jacc.2010.09.080
76. Ronco, C., Haapio, M., House, A. A., Anavekar, N., & Bellomo, R. (2008). Cardiorenal syndrome. *Journal of the American College of Cardiology*, *52*(19), 1527–1539. https://doi.org/10.1016/j.jacc.2008.07.051
77. Metra, M., Cotter, G., Gheorghiade, M., Dei Cas, L., & Voors, A. A. (2012). The role of the kidney in heart failure. *European Heart Journal*, *33*(17), 2135–2142. https://doi.org/10.1093/eurheartj/ehs205
78. Bock, J. S., & Gottlieb, S. S. (2010). Cardiorenal syndrome: New perspectives. *Circulation*, *121*(23), 2592–2600. https://doi.org/10.1161/CIRCULATIONAHA.109.886473
79. Burnett, J. C. Jr, & Knox, F. G. (1980). Renal interstitial pressure and sodium excretion during renal vein constriction. *American Journal of Physiology*, *238*(4), F279–F282. https://doi.org/10.1152/ajprenal.1980.238.4.F279
80. Gori, M., Senni, M., Gupta, D. K., Charytan, D. M., Kraigher-Krainer, E., Pieske, B., et al. (2014). Association between renal function and cardiovascular structure and function in heart failure with preserved ejection fraction. *European Heart Journal*. Advance online publication. https://doi.org/10.1093/eurheartj/ehu254

81. Dries, D. L., Exner, D. V., Domanski, M. J., Greenberg, B., & Stevenson, L. W. (2000). The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. *Journal of the American College of Cardiology*, *35*(3), 681–689. https://doi.org/10.1016/s0735-1097(99)00608-7
82. Fried, L. F., Shlipak, M. G., Crump, C., Kronmal, R. A., Bleyer, A. J., Gottdiener, J. S., et al. (2003). Renal insufficiency as a predictor of cardiovascular outcomes and mortality in elderly individuals. *Journal of the American College of Cardiology*, *41*(8), 1364–1372. https://doi.org/10.1016/s0735-1097(03)00163-3
83. Martin, F. L., McKie, P. M., Cataliotti, A., Sangaralingham, S. J., Korinek, J., Huntley, B. K., et al. (2012). Experimental mild renal insufficiency mediates early cardiac apoptosis, fibrosis, and diastolic dysfunction: A kidney-heart connection. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *302*(2), R292–R299. https://doi.org/10.1152/ajpregu.00194.2011
84. Braunwald, E. (2008). Biomarkers in heart failure. *The New England Journal of Medicine*, *358*(20), 2148–2159. https://doi.org/10.1056/NEJMra0800239
85. Finley, J. J. Jr, Konstam, M. A., & Udelson, J. E. (2008). Arginine vasopressin antagonists for the treatment of heart failure and hyponatremia. *Circulation*, *118*(4), 410–421. https://doi.org/10.1161/CIRCULATIONAHA.108.765289
86. Hammo, Z. S. Y., Almahdawi, Z. M. M., Abbas, S. K., Al-Hermizy, S. M. M., & Tahir, N. T. (2022). Nesfatin-1: As a novel therapeutic agent of congestive heart failure and angina pectoris. Semiconductor Optoelectronics, 41(11), 281–292. https://bdtgd.cn/NESFATIN-1
87. Sapna, F., Raveena, F., Chandio, M., Bai, K., Sayyar, M., Varrassi, G., Khatri, M., Kumar, S., & Mohamad, T. (2023). Advancements in heart failure management: A comprehensive narrative review of emerging therapies. Cureus, 15(10), e46486. https://doi.org/10.7759/cureus.46486
88. Shah, V. K., & Shalia, K. K. (2011). Stem cell therapy in acute myocardial infarction: A pot of gold or Pandora's box. *Stem Cells International*, *2011*, 536758. https://doi.org/10.4061/2011/536758
89. Molla, G., & Bitew, M. (2024). Revolutionizing personalized medicine: Synergy with multi-omics data generation, main hurdles, and future perspectives. *Biomedicines*, *12*(12), 2750. https://doi.org/10.3390/biomedicines12122750
90. Qahwaji, R., Ashankyty, I., Sannan, N. S., Hazzazi, M. S., Basabrain, A. A., & Mobashir, M. (2024). Pharmacogenomics: A genetic approach to drug development and therapy. *Pharmaceuticals*, *17*(7), 940. https://doi.org/10.3390/ph17070940
91. Udoy, I. A., & Hassan, O. (2025). AI-Driven Technology in Heart Failure Detection and Diagnosis: A Review of the Advancement in Personalized Healthcare. Symmetry, 17(3), 469. https://doi.org/10.3390/sym17030469
92. Biondi-Zoccai, G., D'Ascenzo, F., Giordano, S., Mirzoyev, U., Erol, Ç., Cenciarelli, S., Leone, P., & Versaci, F. (2025). Artificial intelligence in cardiology: General perspectives and focus on interventional cardiology. Anatolian Journal of Cardiology, 29(4), 152–163. https://doi.org/10.14744/AnatolJCardiol.2025.5237.