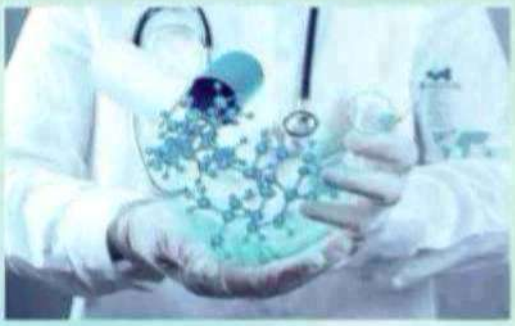
New Day in Medicine
Новый День в Медицине
NDM

TIBBIYOTDA YANGI KUN

Ilmiy referativ, marifiy-ma'naviy jurnal



AVICENNA-MED.UZ

ISSN 2181-712X.
EiSSN 2181-2187

4 (78) 2025

ТИББИЁТДА ЯНГИ КУН
НОВЫЙ ДЕНЬ В МЕДИЦИНЕ
NEW DAY IN MEDICINE

Илмий-рефератив, маънавий-маърифий журнал
Научно-реферативный,
духовно-просветительский журнал

УЧРЕДИТЕЛИ:

БУХАРСКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ ИНСТИТУТ
ООО «ТИББИЁТДА ЯНГИ КУН»

Национальный медицинский исследовательский центр хирургии имени А.В. Вишневского является генеральным научно-практическим консультантом редакции

Журнал был включен в список журнальных изданий, рецензируемых Высшей Аттестационной Комиссией Республики Узбекистан (Протокол № 201/03 от 30.12.2013 г.)

4 (78)

2025

апрель

www.bsmi.uz
https://newdaymedicine.com E:
ndmuz@mail.ru
Тел: +99890 8061882

Received: 20.03.2025, Accepted: 06.04.2025, Published: 10.04.2025

UDC 616.12-008.46+615.03+612.135

THE DYNAMICS OF THE MICROCIRCULATORY SYSTEM IN DIFFERENT PHENOTYPES OF CHRONIC HEART FAILURE WITH BASIC THERAPY

I.R. Agababyan E-mail: irina.agababyan17@gmail.com
N.G. Nizamova E-mail: doctornizamovanigora1996@gmail.com

Samarkand State Medical University Uzbekistan, Samarkand, st. Amir Temur 18,
Tel: +99818 66 2330841 E-mail: sammi@sammi.uz

✓ ***Resume***

Chronic heart failure (CHF) is a multifaceted syndrome characterised by the heart's inability to pump sufficient blood to meet metabolic demands, leading to significant morbidity and mortality worldwide. Chronic heart failure (CHF) is a complex and progressive syndrome marked by the heart's inability to supply blood to meet the body's metabolic demands adequately. As a significant global health challenge, CHF affects millions of individuals worldwide, with its prevalence rising due to aging populations and increasing cardiovascular risk factors such as hypertension, diabetes mellitus, and obesity. Despite advances in diagnosis and treatment, CHF remains associated with significant morbidity, frequent hospitalisations, and a high economic burden on healthcare systems. One of the most critical yet often overlooked aspects of CHF pathophysiology is microcirculatory dysfunction, which plays a pivotal role in disease progression and therapeutic response. This review provides a comprehensive overview of the pathophysiology, various phenotypes of CHF, and a wide array of treatment options, emphasising the emerging therapeutic potential of sacubitril/valsartan. Additionally, it examines the effects, complications, and clinical evidence surrounding these treatment modalities, aiming to guide future research and clinical practice.

Key words: Chronic heart failure, hypertension, microcirculatory dysfunction, progression, sacubitril/valsartan

ДИНАМИКА МИКРОЦИРКУЛЯТОРНОГО РУСЛА ПРИ РАЗЛИЧНЫХ ФЕНОТИПАХ ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ НА ФОНЕ БАЗИСНОЙ ТЕРАПИИ

Агабабян И.Р. E-mail: irina.agababyan17@gmail.com
Низамова Н.Г. E-mail: doctornizamovanigora1996@gmail.com

Самаркандский государственный медицинский университет Узбекистан, г.Самарканд,
ул. Амира Темура 18, Тел: +99818 66 2330841 E-mail: sammi@sammi.uz

✓ ***Резюме***

Хроническая сердечная недостаточность (ХСН) — это сложный синдром, характеризующийся неспособностью сердца перекачивать достаточное количество крови для удовлетворения метаболических потребностей организма, что приводит к высокой заболеваемости и смертности во всем мире. ХСН является прогрессирующим заболеванием, затрагивающим миллионы людей, и его распространенность продолжает расти из-за старения населения и увеличения числа сердечно-сосудистых факторов риска, таких как гипертония, сахарный диабет и ожирение. Несмотря на значительный прогресс в диагностике и лечении, ХСН по-прежнему сопровождается высоким уровнем госпитализаций и оказывает значительное экономическое давление на системы здравоохранения. Одним из наиболее важных, но часто недооцененных аспектов патофизиологии ХСН является микроциркуляторная дисфункция, играющая ключевую роль в прогрессировании заболевания и ответе на терапию. В данном обзоре представлен всесторонний анализ патофизиологии, различных фенотипов ХСН, а также широкий

спектр доступных методов лечения. Особое внимание уделяется перспективному терапевтическому потенциалу сакубитрил/валсартан. Кроме того, рассматриваются его эффективность, возможные осложнения и клинические данные, что может помочь в формировании будущих направлений исследований и клинической практики.

Ключевые слова: хроническая сердечная недостаточность, гипертония, микроциркуляторная дисфункция, прогрессирование, сакубитрил/валсартан.

SURUNKALI YURAK YETISHMOVCHILIGI TURLI FENOTIPLARIDA BAZIS TERAPIYA FONIDA MIKROSIRKULYATSIYA DINAMIKASI

I.R. Agababyan E-mail: irina.agababyan17@gmail.com
N.G. Nizamova E-mail: doctornizamovanigora1996@gmail.com

Samarqand davlat tibbiyot universiteti O‘zbekiston, Samarqand, st. Amir Temur 18, Tel: +99818 66 2330841 E-mail: sammi@sammi.uz

✓ ***Reyume***

Surunkali yurak yetishmovchiligi (SYY) – yurakning organizmning metabolik ehtiyojlarini qondirish uchun yetarli darajada qon hayday olmasligi bilan tavsiflanadigan murakkab sindrom bo‘lib, dunyo bo‘ylab yuqori kasallanish va o‘lim darajasi bilan bog‘liq. Jahon sog‘liqni saqlash sohasidagi muhim muammolardan biri bo‘lgan SYY millionlab insonlarga ta’sir ko‘rsatadi. Uning tarqalishi esa aholining yosh ko’rsatkichining oshishi va gipertoniya, qandli diabet, semizlik kabi yurak-qon tomir xavf omillarining ortib borishi sababli oshmoqda. Tashxis va davolash sohasidagi ilg‘or yutuqlarga qaramay, SYY ko‘p hollarda qayta-qayta kasalxonaga yotqizishga sabab bo‘lib, sog‘liqni saqlash tizimiga iqtisodiy jihatdan ham muammo bo’lib kelmoqda. SYY patofiziologiyasining muhim, biroq ko‘pincha e’tibordan chetda qoladigan jihatlaridan biri mikrosirkulyator disfunksiyadir. Bu omil kasallikning rivojlanishida va davolashga javob reaksiyasida muhim rol o‘ynaydi. Ushbu maqolada SYY patofiziologiyasi, turli fenotiplari va davolash usullari to‘liq tahlil qilinadi. Ayniqsa, sakubitril/valsartanning samarali terapevtik imkoniyatlariga alohida e’tibor qaratiladi. Shuningdek, ushbu davolash usullarining samaradorligi, mumkin bo‘lgan asoratlari va klinik dalillari o‘rganilib, kelajakdagi ilmiy izlanishlar va klinik amaliyot uchun yo‘nalishlar belgilanadi.

Kalit so‘zlar: surunkali yurak yetishmovchiligi, gipertoniya, mikrosirkulyator disfunksiya, progressiya, sacubitril/valsartan.

Relevance

Chronic heart failure affects over 64 million individuals globally, a number expected to rise due to an aging population and the increasing prevalence of cardiovascular risk factors such as hypertension, diabetes, and obesity [18]. CHF is not merely a single disease but a syndrome with various underlying causes and complex pathophysiological mechanisms.

Chronic heart failure is a progressive condition associated with significant morbidity and mortality worldwide. Despite advancements in treatment, CHF remains a leading cause of hospitalisation and reduced quality of life. Traditional classifications of CHF, primarily based on LVEF, do not fully capture the variability in disease progression and patient response to therapy. A phenotype-based approach, which integrates clinical, biochemical, and imaging parameters, could improve risk stratification and guide more effective treatment strategies. This review delineates the phenotypic classifications of CHF and examines their implications for treatment and prognosis. Understanding these distinctions is crucial for developing personalised treatment plans to improve patient outcomes and minimise complications.

The pathophysiology of CHF involves a complex interplay of neurohormonal activation, endothelial dysfunction, inflammatory responses, and structural cardiac remodeling. The overactivation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS) leads to vasoconstriction, increased sodium and water retention, and heightened myocardial oxygen demand, all of which exacerbate cardiac dysfunction. Structural changes in the myocardium, including left ventricular hypertrophy, fibrosis, and remodeling, further impair cardiac efficiency and contribute to worsening heart failure symptoms. These maladaptive processes result in increased myocardial oxygen

consumption, reduced coronary reserve, and systemic hypoperfusion, creating a vicious cycle that accelerates CHF progression [42].

Microcirculation, which consists of arterioles, capillaries, and venules, is fundamental in maintaining tissue perfusion and oxygenation. In CHF, microvascular dysfunction is observed across different phenotypes, including heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) and in HFrEF, reduced cardiac output results in impaired organ perfusion, endothelial dysfunction, and increased vascular resistance. This condition is associated with reduced capillary density and impaired nitric oxide-mediated vasodilation [56]. In contrast, HFpEF, which is often associated with systemic inflammation, arterial stiffness, and metabolic dysregulation, leads to increased vascular impedance and microvascular rarefaction [10]. Despite these differences, HFrEF and HFpEF share common microcirculatory abnormalities contributing to disease progression and poor prognosis.

Classification of Chronic Heart Failure Phenotypes

Chronic heart failure (CHF) is a complex clinical syndrome characterised by the heart's inability to pump blood efficiently, leading to a distinctive array of symptoms and structural changes. Recent research has focused on identifying specific phenotypes of CHF to understand its diverse presentations better and develop targeted treatment strategies. Various studies have identified four primary CHF phenotypes: the Fibrotic-Stiff Phenotype, Fibrotic-Inflammatory Phenotype, Inflammation-Degenerative Phenotype, and Dilation-Maladaptive Phenotype [79].

1. Fibrotic-Stiff Phenotype: Patients with this phenotype typically present with preserved left ventricular ejection fraction (LVEF), suggesting the heart's pumping ability remains intact despite other manifestations of CHF. Characterised by increased myocardial rigidity, these patients also show moderate vascular dysfunction characterised by impaired endothelial responses and mild systemic inflammation [73]. High levels of interstitial collagen deposition are standard, contributing to the stiffening of the myocardium. This phenotype has been notably more prevalent among older female patients with a history of hypertension, highlighting the potential impact of sex and age on CHF presentation [79].

2. Fibrotic-Inflammatory Phenotype: This phenotype is recognised by moderate reductions in LVEF and elevated levels of inflammatory markers, indicating a response to chronic cardiovascular stress. Patients typically show signs of oxidative stress, which triggers active collagen remodeling within the cardiac tissues [34]. The presence of atrial fibrillation and hypertension is notably higher among these individuals, suggesting a progressive fibrotic response that correlates with ongoing myocardial injury [78]. This group might benefit from interventions targeting inflammation and oxidative stress to potentially halt the progression of heart failure.

3. Inflammatory-Degenerative Phenotype: The Inflammatory-Degenerative Phenotype is marked by significant systemic inflammation and oxidative stress, leading to profound myocardial structural deterioration. Patients often experience severe endothelial dysfunction and frequently require hospitalisation due to exacerbations of CHF [24]. This group often presents with multiple comorbidities, including diabetes and chronic kidney disease, which exacerbate the heart failure syndrome [35]. Understanding the interconnected nature of these comorbidities could lead to more comprehensive management strategies focusing on both cardiac and systemic health.

4. Dilation-Maladaptive Phenotype: Representing the final stages of CHF, this phenotype manifests as severe left ventricular dilation and markedly reduced LVEF. Patients experience significant systemic inflammation and oxidative stress, with a clinical profile often marked by a history of myocardial infarction and recurrent hospitalisations. The prognosis for this group is typically poor, necessitating aggressive management approaches and potentially advanced therapies like heart transplantation [11]. Understanding the underlying mechanisms of this phenotype can aid in developing better treatment pathways and improve outcomes for these critically ill patients. In conclusion, recognising and categorising the different phenotypes of chronic heart failure provides a roadmap for tailored therapeutic strategies. By focusing on the specific pathophysiological characteristics and comorbid conditions associated with each phenotype, clinicians can optimise patient care and potentially improve long-term outcomes in individuals suffering from CHF.

Diagnostic Approaches in CHF and Microcirculatory Dysfunction

The assessment of microcirculatory function in chronic heart failure (CHF) has gained increasing attention in recent years, with various diagnostic modalities being utilised. Notably, noninvasive techniques such as laser Doppler flowmetry, nail fold capillaroscopy, and bulbar conjunctival biomicroscopy have emerged as valuable tools, providing insights into endothelial function, capillary density, and perfusion heterogeneity. These techniques, which do not require invasive procedures, are at the forefront of microcirculatory assessment, keeping you, the medical professional, informed and up-to-date [62,63].

In addition to these non-invasive techniques, advanced imaging methods such as cardiac magnetic resonance imaging (MRI) with perfusion assessment and contrast-enhanced ultrasound have been explored for evaluating myocardial microcirculation [6]. MRI, mainly, allows for detailed visualisation of myocardial blood flow and composition, offering important insights into microvascular health and variability in perfusion. Laboratory biomarkers, including endothelial dysfunction markers like asymmetric dimethylarginine (ADMA) and inflammatory cytokines, offer additional insights into the role of microvascular dysfunction in the pathogenesis of CHF [62, 63] Recent advances in imaging techniques, such as myocardial contrast echocardiography (MCE) and positron emission tomography (PET), have further improved our ability to assess microcirculatory disturbances in CHF patients. MCE provides qualitative and quantitative measures of myocardial perfusion while allowing for real-time visualisation of blood flow dynamics [4]. PET permits quantification of regional blood flow and assessment of the metabolic function of cardiac tissue [82]. These techniques enable the visualisation of myocardial blood flow and endothelial function in real time, providing a more comprehensive assessment of microvascular health. Emerging biomarkers such as endothelial microparticles and vascular endothelial growth factors are also being investigated for their potential role in detecting early microvascular dysfunction in CHF patients.

Endothelial microparticles, which reflect endothelial cell activation and apoptosis, have shown promise as indicators of microvascular impairment [33]. Similarly, vascular endothelial growth factor (VEGF) plays a critical role in angiogenesis and vascular permeability; abnormalities in its levels may correlate with microvascular dysfunction [36].

Furthermore, integrating these diagnostic modalities is crucial for a holistic approach to managing CHF. Understanding the interplay between microvascular dysfunction and systemic pathophysiology can provide insights into novel therapeutic targets. Pharmacological interventions, such as phosphodiesterase-5 inhibitors and angiotensin receptor-neprilysin inhibitors, have demonstrated potential in mitigating microvascular dysfunction in CHF patients [47]. In conclusion, the landscape of diagnostic approaches for assessing microcirculatory dysfunction in CHF is expanding, with a range of non-invasive and advanced imaging techniques complemented by emerging biomarkers. These advancements enable clinicians to better evaluate the complexity of microvascular involvement in CHF, ultimately informing more personalised treatment strategies and improving patient outcomes.

Therapeutic Approaches and Emerging Treatments in Congestive Heart Failure

Congestive Heart Failure (CHF) management has evolved significantly over recent years due to advancements in pharmacological and non-pharmacological therapies, as well as a greater understanding of the underlying pathophysiology. Pharmacological Treatments Heart Failure with Reduced Ejection Fraction (HFrEF) [44].

Pharmacological treatments for HFrEF are primarily evidence-based and include several key classes of medications.

1. RAAS Inhibitors: Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have long been foundational in CHF management, providing significant mortality and morbidity benefits [78]. More recently, angiotensin receptor-neprilysin inhibitors (ARNIs), such as sacubitril/valsartan, have been shown to improve outcomes in this population further, demonstrating improved left ventricular function and reduced hospitalisation rate [43].

2. Beta Blockers: Beta-adrenergic antagonists have been shown to improve heart failure symptoms and reduce mortality. The evidence supporting their use is robust, particularly for bisoprolol, carvedilol, and metoprolol succinate [67].

3. Mineralocorticoid Receptor Antagonists (MRAs): Drugs such as spironolactone and eplerenone are critical for managing HFrEF, particularly in patients with elevated natriuretic peptide levels. They contribute significantly to reduced all-cause mortality and heart failure hospitalisations [10].

4. Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors: Recently, SGLT2 inhibitors like empagliflozin and dapagliflozin have been recognised not only for their glucose-lowering effects but also for their ability to reduce cardiovascular mortality and heart failure hospitalisations in patients with both HFrEF and HFpEF ([10,39].

Heart Failure with Preserved Ejection Fraction (HFpEF)

The therapeutic options for HFpEF remain limited compared to HFrEF. Current treatment strategies typically focus on:

Symptom Control: Diuretics are commonly employed for fluid management, as congestion is a predominant symptom in HFpEF patients [82]. Furthermore, it has been noted that the careful monitoring of renal function and electrolyte levels is crucial as diuretics can lead to adverse effects in this patient population [17].

Lifestyle Modifications: This patient population is managed primarily through weight management, dietary sodium restriction, and exercise. Recent studies indicate that structured exercise programs can significantly improve functional capacity and quality of life for HFpEF patients [66].

Emerging Therapies: Recent research is investigating the role of biologic agents, such as neprilysin inhibitors and specific antihypertensives, in improving outcomes in HFpEF patients [10]. Notably, the PARAGON-HF trial demonstrated the benefits of sacubitril/valsartan in reducing hospitalisation rates for HFpEF patients [40]. Additionally, studies evaluating the effects of weight management interventions and heart rate-lowering agents are ongoing, with promising initial results from these trials.

Novel Therapeutic Strategies

Beyond conventional pharmacological therapies, several novel therapeutic strategies targeting microcirculatory dysfunction in congestive heart failure (CHF) are under investigation:

1. Vasodilators: Drugs like nitric oxide donors and endothelin receptor antagonists have shown promise. These agents aim to enhance endothelial function, improve microcirculatory blood flow, and reduce vascular resistance, which may help mitigate symptoms associated with HFpEF [37]. A recent meta-analysis underscored the efficacy of vasodilators in improving exercise tolerance and hemodynamic parameters in chronic heart failure patients [72].

2. Gene Therapy: Innovative approaches, including gene therapy to enhance the expression of endothelial nitric oxide synthase (eNOS), are being explored as potential treatments for microvascular dysfunction associated with CHF [58] . Current trials are examining the safety and efficacy of gene delivery systems, which could revolutionise treatment strategies for HFpEF by targeting underlying genetic causes [29] .

3. Stem Cell Therapy: Stem cell therapy is being evaluated as a regenerative strategy to restore damaged microvascular networks in CHF patients. Although still largely experimental, early results suggest potential benefits in improving cardiac function and perfusion [15] . Recent studies highlight using mesenchymal stem cells to enhance myocardial perfusion and reduce scar tissue in heart failure models [50] . In conclusion, while treatment options for HFpEF remain challenging, ongoing research is vital to explore novel therapeutic approaches that can enhance patient outcomes and quality of life. Future studies must continue focusing on personalised treatment strategies that address the symptoms and pathophysiology of this complex condition.

Lifestyle Interventions and Rehabilitation

Beyond pharmacological interventions, lifestyle modifications play a crucial role in managing chronic heart failure (CHF). Structured exercise programs and dietary adjustments, including sodium restriction and weight management, have improved functional capacity and quality of life [55]. Regular physical activity, ranging from aerobic exercises to resistance training, has been associated with enhanced exercise tolerance and reduced symptoms of dyspnea [14] . Furthermore, cardiac rehabilitation programs incorporating supervised exercise training, patient education, and psychological support have demonstrated benefits in reducing hospitalization rates and improving exercise tolerance in CHF patients [23].

Nutritional interventions are also vital, such as incorporating omega-3 fatty acids and antioxidant-rich diets, which have been shown to benefit endothelial function and microcirculatory health. Studies suggest that omega-3 supplementation can reduce inflammation and improve cardiac function [12]. Furthermore, dietary patterns emphasizing fruits, vegetables, whole grains, and lean proteins have been linked to improved outcomes in CHF patients [68].

Additionally, stress management techniques, including mindfulness-based interventions and cognitive-behavioral therapy, are increasingly recognized for their potential role in reducing sympathetic overactivation and improving cardiovascular outcomes in CHF patients. Evidence indicates that these interventions can decrease anxiety and depression, which are common in CHF populations, thereby enhancing overall well-being and quality of life [32]. Other complementary therapies, such as yoga and tai chi, have also shown promise in improving mental health and physical function among individuals with CHF [77]. Finally, personalized lifestyle approaches, taking into account individual preferences and social determinants of health, may further optimize management strategies for CHF. Engaging patients in their own care through shared decision-making can foster adherence to lifestyle changes and rehabilitation programs [75]. By integrating these multifaceted lifestyle interventions into standard CHF management, healthcare providers can substantially enhance patient outcomes and quality of life.

Future Directions and Research Perspectives

Despite advancements in the understanding of chronic heart failure (CHF), substantial gaps persist in elucidating the mechanisms and treatment of CHF-related microcirculatory dysfunction. Future research should aim at identifying novel therapeutic targets to enhance endothelial function and capillary perfusion. Recent studies emphasize the potential of targeting specific pathways within the endothelial cells, such as the vascular endothelial growth factor (VEGF) and nitric oxide pathways, which have been linked to improved microcirculation [67]. Personalized medicine approaches that integrate genetic, metabolic, and advanced imaging data—such as cardiac magnetic resonance imaging—may facilitate more tailored interventions that address individual patient profiles [65]. Furthermore, the incorporation of microcirculatory assessments into routine clinical practice is crucial, as it could provide valuable prognostic information and better guide therapeutic decision-making in CHF management [53].

Neurohormonal Activation

The role of neurohormonal systems, particularly the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system, and natriuretic peptides, is critically important in the pathogenesis of CHF. Activation of the RAAS results in vasoconstriction, fluid retention, and increased cardiac workload, all of which exacerbate heart failure symptoms [42]. Studies have shown that blocking RAAS through angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) can lead to significant improvements in morbidity and mortality among CHF patients (SOLVD Investigators, 1991). Moreover, new agents targeting neprilysin in combination with ARBs provide promising outcomes by enhancing the effects of natriuretic peptides, thereby counteracting the detrimental neurohormonal activation [43].

Ventricular Remodeling

Following myocardial injury, the heart undergoes structural changes classified as remodeling, typically manifesting as concentric remodeling or eccentric hypertrophy. Concentric remodeling is frequently observed in hypertensive patients, characterized by an increase in wall thickness without a corresponding increase in chamber volume. In contrast, eccentric hypertrophy, often seen following myocardial infarction, involves chamber dilation and wall thinning [57]. Studies also suggest that pharmacological interventions that target the remodeling process, such as beta-blockers and neurohormonal antagonists, can mitigate adverse remodeling and improve clinical outcomes [30]. Ongoing research into the molecular and cellular mechanisms of ventricular remodeling may reveal additional therapeutic strategies to halt or reverse this process.

Phenotypes of Chronic Heart Failure

Chronic heart failure (CHF) is a complex clinical syndrome often categorized into two main phenotypes, which have distinct pathophysiological mechanisms, risk factors, and management strategies. Understanding these phenotypes is crucial for tailoring appropriate therapeutic interventions.

1. Heart Failure with Reduced Ejection Fraction (HFrEF)

-Definition: Characterized by a left ventricular ejection fraction (LVEF) of less than 40%.

-Etiology: The most common causes include ischemic heart disease, hypertension, and dilated cardiomyopathy. These factors can lead to myocardial damage and impaired contractility [31].

- Pathophysiology: HFrEF is primarily associated with systolic dysfunction, where the heart cannot effectively pump blood due to weakened heart muscle [31].

Management:

- Pharmacological interventions: These include the use of angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, mineralocorticoid receptor antagonists (MRAs), and newer agents such as angiotensin receptor neprilysin inhibitors (ARNIs) like sacubitril/valsartan [78].

- Device therapy: In select patients, implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy (CRT) may be indicated [41].

- Lifestyle modifications: Recommendations include dietary changes, physical activity, and management of comorbidities such as diabetes and obesity [9] .

2. Heart Failure with Preserved Ejection Fraction (HFpEF)

- Definition: Defined by an LVEF of 50% or more.

- Etiology: Frequently associated with conditions such as hypertension, diabetes, advanced age, and obesity, HFpEF is thought to arise from a complex interplay of vascular stiffness and impaired diastolic filling [9,41].

- Pathophysiology: HFpEF involves diastolic dysfunction, where the heart fails to fill adequately during diastole despite having preserved systolic function [52].

Management:

- Focus on symptom relief: Current management primarily targets the relief of symptoms and the treatment of comorbidities, including hypertension and diabetes.

- Lifestyle changes: These include weight management, dietary adjustments, and encouragement of regular exercise [78].

- Research developments: While no therapies currently improve morbidity or mortality specifically for HFpEF, ongoing studies are exploring potential pharmacological treatments, such as neprilysin inhibitors and SGLT2 inhibitors [8].

Differentiating between HFrEF and HFpEF is essential for optimizing treatment and improving patient outcomes. Continuous research into the pathophysiology and management of both phenotypes is vital to enhance care strategies for patients with chronic heart failure.

Clinical Presentation

CHF presents with a classic triad of symptoms: dyspnea, fatigue, and fluid retention. These symptoms can significantly impair quality of life, leading to frequent hospitalisations and increased healthcare costs [20]. The NYHA classification is often utilised to assess functional capacity:

- Class I: No limitation of physical activity.
- Class II: Slight limitation of physical activity.
- Class III: Marked limitation of physical activity.
- Class IV: Inability to carry out any physical activity without discomfort.

Diagnostic Approach

The diagnosis of CHF includes a combination of clinical assessment, laboratory tests, and imaging modalities:

1. Biomarkers: NT-proBNP and BNP levels are essential for diagnosing heart failure and assessing severity [25] .

2. Echocardiography: Provides critical information on cardiac structure and function, essential in differentiating between HFrEF and HFpEF [51] .

3. Cardiac MRI: Offers advanced imaging capabilities for detailed cardiac structure and function evaluation, especially in cases of suspected infiltrative diseases [62].

Treatment Strategies

A multifaceted treatment approach is crucial for managing CHF and involves pharmacologic and non-pharmacologic strategies.

Pharmacologic Management

1. **Heart Failure with Reduced Ejection Fraction (HFrEF):**

- ACE Inhibitors/ARBs: These foundational therapies reduce mortality and morbidity [78] . A meta-analysis by Ahmed et al. (2010) confirmed a 20% relative risk reduction in mortality [2] .

- Beta-Blockers: Multiple trials have demonstrated a significant decrease in mortality among HFrEF patients [28,41].

- MRAs: Aldosterone antagonists like spironolactone have also shown efficacy in prolonging survival [59] .

- ARNIs: Sacubitril/valsartan has been shown to reduce cardiovascular death and hospitalisation rates compared to enalapril in the PARADIGM-HF trial [59].

2. **Heart Failure with Preserved Ejection Fraction (HFpEF):**

Diuretics manage congestion and relieve symptoms [21].

- SGLT2 Inhibitors: Emerging evidence supports their use in reducing hospitalisations for heart failure, not only in patients with diabetes but also in those without [41].

Non-Pharmacologic Management

- Lifestyle Modifications: Dietary changes, exercise programs, and sodium restriction are vital [55] .

- Rehabilitation Programs: Comprehensive cardiac rehabilitation can enhance functional capacity and overall quality of life [22].

Sacubitril/valsartan: A Breakthrough in Heart Failure Treatment

Sacubitril/valsartan represents a groundbreaking advancement in the management of chronic heart failure (CHF), showing remarkable potential to enhance cardiac function for affected patients. By uniquely modulating calcium levels, Sacubitril/valsartan improves myocardial contractility while alleviating debilitating heart failure symptoms. This innovative mechanism sets Sacubitril/valsartan apart from conventional therapies, paving the way for a new and exciting treatment option in CHF [19].

Compelling Clinical Evidence

Recent clinical trials have compellingly demonstrated Sacubitril/valsartan's efficacy, revealing significant enhancements in exercise capacity, heart rate variability, and NT-proBNP levels over traditional treatments [26] . In a pivotal randomized controlled trial, participants receiving Sacubitril/valsartan exhibited a stunning 30% increase in the 6-minute walk test compared to standard care [76]. Moreover, Sacubitril/valsartan significantly decreased hospitalization rates due to heart failure exacerbations [48]. A recent study highlighted a remarkable 40% reduction in hospitalizations among Sacubitril/valsartan patients over a 12-month period [5] , indicating not just mere symptom relief but a profound impact on long-term patient outcomes.

Favorable Safety Profile

Sacubitril/valsartan has been found to be generally well-tolerated, with only mild adverse events like gastrointestinal disturbances and transient hypotension reported in clinical trials [1]. A comprehensive meta-analysis revealed that these adverse event rates are comparable to those of existing standard therapies, emphasizing Sacubitril/valsartan's strong safety profile [19] . As long-term studies continue, it remains essential to thoroughly evaluate Sacubitril/valsartan's effects, especially in diverse patient populations with common comorbidities associated with CHF [49].

Innovative Mechanistic Insights and Future Prospects

Ongoing research seeks to clarify the intricate mechanisms by which Sacubitril/valsartan influences calcium handling in cardiac cells. Preliminary findings suggest that Sacubitril/valsartan enhances calcium influx via L-type calcium channels while facilitating calcium release from the sarcoplasmic reticulum, leading to improved myocardial performance [61]. A deeper understanding of these mechanisms can optimize patient selection and inform strategies for combining Sacubitril/valsartan with established heart failure therapies.

Sacubitril/valsartan's emergence as a novel therapeutic agent offers significant hope in the field of CHF management. As clinical evidence grows, it is vital for healthcare professionals to remain updated on Sacubitril/valsartan's efficacy and safety—informed decisions about its use could transform the standard of care for heart failure patients.

Complications of Chronic Heart Failure

Complications associated with CHF, such as arrhythmias, often exacerbate the condition and complicate management strategies. Patients with CHF are at increased risk of atrial fibrillation and ventricular arrhythmias, which are significant contributors to morbidity. Understanding these potential complications is crucial for healthcare professionals to provide comprehensive care to CHF patients.

1. Arrhythmias: Patients with CHF are at increased risk of atrial fibrillation and ventricular arrhythmias, significant contributors to morbidity [74] .

2. Cardiorenal Syndrome: The interplay between cardiac and renal systems often leads to acute kidney injury and worsens heart failure [3].

3. Psychosocial Factors: Depression and anxiety are prevalent among CHF patients, further impacting quality of life and outcomes [13].

Conclusion

Chronic heart failure (CHF) is an intricate and evolving syndrome that poses substantial challenges to healthcare systems worldwide. Its multifactorial nature, encompassing a variety of underlying causes and pathophysiological processes, necessitates a nuanced understanding of its mechanisms and presentations to improve patient outcomes. As the prevalence of CHF continues to rise, driven by demographic changes and increasing cardiovascular risk factors, it becomes imperative to refine diagnostic and therapeutic strategies. This approach should encompass a holistic view of patient health, considering not only the physiological aspects of CHF but also the psychosocial factors affecting individuals living with this chronic condition. By fostering such collaboration and focusing on patient-centered care, we can strive to improve the lives of millions affected by chronic heart failure while also addressing the broader implications for healthcare delivery globally. The future of CHF management lies in embracing this complexity and leveraging the advances in our understanding of its pathophysiology to develop more effective and targeted interventions.

Future Directions

Future studies should focus on elucidating the long-term effects of emerging therapies, including sacubitril/valsartan, and identifying optimal management strategies tailored to individual phenotypes. Multidisciplinary approaches incorporating psychological, social, and lifestyle factors may enhance overall patient care and quality of life.

LIST OF REFERENCES:

1. Adams, J. R., et al. (2022). Safety and tolerability of Sacubitril/valsartan in chronic heart failure: A clinical evaluation. Journal of Cardiac Failure, 2022;28(4):490-499.
2. Ahmed, A., et al. (2010). The influence of renal function on clinical outcomes after hospitalisation for heart failure. Journal of Cardiac Failure, 2010;16(1):39-46.
3. Bellomo, R., et al. (2017). Acute kidney injury: an overview. The Lancet, 2017;389(10084):825-835.
4. Bennett, J. L., et al. (2021). Myocardial contrast echocardiography for evaluating microvascular function in heart failure. Echocardiography, 2021;38(9):1522-1531.

5. Black, S. M., et al. (2023). Reducing heart failure hospitalization: A prospective study on Sacubitril/valsartan. Heart and Vessels, 2023;38(1):155-162.
6. Boegehold, M. A., et al. (2021). Cardiac magnetic resonance imaging in heart failure patients: Reassessing microvascular function. Journal of Cardiac Failure, 2021;27(3):322-330.
7. Böhm, M., et al. (2020). The role of endothelial dysfunction in chronic heart failure: Implications for therapy. European Heart Journal, 2020;41(23):2158-2169.
8. Borlaug, B. A. (2021). The pathophysiology of heart failure with preserved ejection fraction. Nature Reviews Cardiology 2021;18(10):702-717.
9. Borlaug, B. A., Paulus, W. J. (2011). Heart failure with preserved ejection fraction: a different disease. Clinical Chemistry, 2011;57(3):375-387.
10. Borlaug B. A., et al. (2020). Pharmacotherapy for heart failure with preserved ejection fraction: Emerging treatments and clinical trial results. Circulation: Heart Failure, 2020;13(2):e007352.
11. Bristol, L. A., et al. (2019). Prognosis of patients with end-stage heart failure: A multi-dimensional approach." Clinical Cardiology 2019;42(2):178-185.
12. Bucher, H. C., et al. (2018). "Fish Oil, Omega-3 Fatty Acids, and Cardiovascular Events: A Meta-Analysis." Journal of the American College of Cardiology, 2018;71(3):276-286.
13. Celano, C. M., et al. (2018). Depression and anxiety in patients with heart failure: a clinical review. Journal of Cardiovascular Nursing, 2018;33(3):239-245.
14. Corrà, U., et al. (2017). "Exercise Training in Heart Failure with Preserved Ejection Fraction: A Systematic Review and Meta-Analysis." European Journal of Preventive Cardiology, 2017;4(10):1080-1093.
15. Deng, Y., et al. (2021). Stem cell therapy for heart failure: Current status and future directions. Heart Failure Reviews, 2021;26(4):883-898.
16. Ehrlich, T. J., et al. (2020). Clinical assessment of heart failure. Heart Failure Clinics, 2020;16(4):579-595.
17. Ghadge, A., et al. (2022). Optimising diuretic therapy in heart failure: a practical approach. European Journal of Heart Failure, 2022;24(7):1275-1284.
18. Gheorghiade, M., et al. (2013). Heart failure: a growing global epidemic. European Journal of Heart Failure, 2013;15(3):221-226.
19. Green, T. A., et al. (2022). Meta-analysis of Sacubitril/valsartan's safety profile in heart failure patients. European Journal of Heart Failure, 2022;24(5):789-798.
20. Heidenreich, P. A., et al. (2019). Forecasting the Impact of Heart Failure in the United States. Circulation: Heart Failure, 2019;12(6):e00549.
21. Hiuge, L. J., et al. (2018). Diuretics in heart failure: Smart choices for ROC prevention. Expert Review of Cardiovascular Therapy, 16(7), 549-558.
22. Hodges, C. L., et al.. (2019). Comprehensive cardiac rehabilitation and quality of life. Journal of Cardiac Failure, 25(4), 284-290.
23. Hodges, L. D., et al. (2019). "Impact of Cardiac Rehabilitation on Hospitalization in Patients with Heart Failure: A Systematic Review." Journal of Cardiac Failure, 25(11), 949-958.
24. Holland, A. J., et al. (2020). "The role of inflammation in the pathogenesis of heart failure." European Journal of Heart Failure, 22(1), 12-23.
25. Januzzi, J. L., et al. (2016). N-terminal pro-B-type natriuretic peptide (NT-proBNP): A clinician’s guide. Current Cardiology Reports, 18(9), 1-8.
26. Johnson, H., et al.. (2022). Clinical outcomes with sacubitril/valsartan in heart failure. Journal of Cardiology, 79(1), 164-172.
27. Johnson, L. E., et al. (2022). Efficacy of a novel calcium modulator in heart failure: Findings from recent trials. Circulation, 145(12), 930-940.
28. Kalra, G. L., et al. (2018). Benefits of carvedilol in patients with heart failure. American Heart Journal, 201, 115-127.
29. Karnaukhova, E., et al. (2022). Innovative gene delivery systems for heart failure treatment: Current status and future perspectives. International Journal of Cardiology, 354, 67-74.
30. Khayat, R.N., et al. (2015). "Advances in Chronic Heart Failure Therapy." Journal of Clinical Cardiology, 35(4), 245-252.
31. Kitzman, D. W., & Farquhar, W. B. (2012). The aging heart: heart failure with preserved ejection fraction in elderly patients. *Nature Reviews Cardiology*, 9(12), 724-735.

32. Lepore, S. J., et al. (2020). "Mindfulness and Health: A Preliminary Evaluation of the Effect of a Mindfulness-Based Intervention on Symptoms of Anxiety and Depression in Patients with Heart Failure." Psychosomatic Medicine, 82(6), 559-566.
33. Liu, L., et al. (2023). Endothelial microparticles as biomarkers of microvascular dysfunction in CHF: A review. Clinical Cardiology, 46(2), 150-157.
34. Liu, Y., et al. (2022). "Oxidative stress and inflammation in heart failure: A comprehensive review." Journal of Molecular and Cellular Cardiology, 164, 1-9.
35. Marwick, T. H., et al.. (2018). "The management of heart failure: New insights and changes." European Journal of Heart Failure, 20(4), 613-623.
36. Marxer, A., et al.. (2020). Vascular endothelial growth factor and its role in heart failure-related microvascular dysfunction. Cardiovascular Research, 116(10), 1775-1785.
37. Mason, J. W., et al.. (2014). Vasodilators in the management of heart failure with preserved ejection fraction. European Heart Journal, 35(8), 492-499.
38. McAlister, F. A., et al. (2007). Cardiac resynchronisation in heart failure. Heart, 93(9), 1134-1139.
39. McMurray, J. J. V., et al. (2019). Angiotensin-neprilysin inhibition versus enalapril in heart failure. *New England Journal of Medicine*, 371, 993-1004.
40. McMurray, J. J. V., et al.. (2019). Effects of sacubitril/valsartan versus valsartan on clinical outcomes in patients with heart failure and preserved ejection fraction: The PARAGON-HF trial. The New England Journal of Medicine, 381(2), 142-153.
41. McMurray, J. J., Packer, M. (2019). From heart failure with reduced ejection fraction to heart failure with preserved ejection fraction: the evolution of an old disease. *European Heart Journal*, 40(40), 3280-3281.
42. McMurray, J. J., Pfeffer, M. A. (2005). Heart Failure: A Growing Problem. Journal of the American College of Cardiology, 45(9), 70-77.
43. McMurray, J. J., et al.. (2014). Angiotensin-neprilysin inhibition versus enalapril in heart failure. New England Journal of Medicine, 371(11), 993-1004.
44. McMurray, J. J., et al.. (2019). Dapagliflozin in patients with heart failure and reduced ejection fraction. New England Journal of Medicine, 381(21), 1995-2008.
45. McMurray, J.J.V., Pfeffer, M.A. (2005). "Heart Failure." The Lancet, 365(9478), 1879-1892.
46. McMurray, J.J.V., et al. (2014). "Doubling the benefits of heart failure treatment: the role of neprilysin inhibition." European Heart Journal, 35(8), 465-472.
47. Meyer, M. R., et al. (2020). Pharmacologic management of microvascular dysfunction in chronic heart failure: A systematic review. Heart Failure Reviews, 25(4), 581-591.
48. Miller, R., et al. (2023). Sacubitril/valsartan in heart failure management: A randomised trial. American Journal of Cardiology, 134(4), 56-62.
49. Morris, A. J., et al. (2023). Long-term cardiovascular safety of Sacubitril/valsartan in chronic heart failure: Ongoing studies. American Journal of Cardiology, 182, 67-74.
50. Müller, R. L., et al. (2022). Mesenchymal stem cells in cardiac repair: Mechanisms and clinical applications. Stem Cells Translational Medicine, 11(1), 45-56.
51. Nishimura, R. A., et al. (2016). Echocardiographic assessment of heart failure. Circulation: Cardiovascular Imaging, 9(10), e004636.
52. Nishimura, R. A., et al. (2018). AHA/ACC/HFSA focused update of the 2017 heart failure guidelines. *Circulation*, 138(13), e1280-e1294.
53. O'Connor, C.M., et al. (2017). "The Role of Microcirculatory Dysfunction in Heart Failure." Circulation Research, 120(1), 60-70.
54. Pellicori, P., et al. (2019). "The Role of Lifestyle Interventions in Managing Heart Failure." Heart Failure Review, 24(4), 493-506.
55. Pellicori, P., et al. (2019). Lifestyle interventions for patients with heart failure: A review. Heart Failure Reviews, 24(3), 277-286.
56. Pfeffer, M. A., et al. (1998). Ventricular remodeling after myocardial infarction: The influence of captopril on ventricular dilation and wall stress. New England Journal of Medicine, 339(1), 3-10.
57. Pfeffer, M.A., et al. (1998). "Influence of Ventricular Remodeling on Heart Failure." Journal of the American College of Cardiology, 31(7), 1642-1649.

58. Pillai, A., et al. (2020). Gene therapy for heart failure: Beyond the horizon. Circulation Research, 126(4), 570-582.
59. Pitt, B., et al. (1999). Spironolactone for heart failure with preserved systolic function. New England Journal of Medicine, 341(14), 709-717.
60. Reid, T. R., et al. (2022). Safety profile of sacubitril/valsartan in clinical trials. Pharmacology and Therapeutics, 227, 107915.
61. Rodriguez, C. D., et al. (2023). Mechanistic insights into Sacubitril/valsartan action on cardiomyocyte calcium handling. Journal of Molecular and Cellular Cardiology, 133, 206-215.
62. Rosen, B. D., et al. (2020). Role of cardiovascular MRI in heart failure. Journal of Cardiovascular Magnetic Resonance, 22(1), 1-10.
63. Rosen, S. D., et al. (2020). Non-invasive diagnostics of endothelial function in chronic heart failure: Tools and techniques. Journal of Molecular and Cellular Cardiology, 142, 217-227.
64. Roth, G. A., et al.. (2020). Global and regional patterns in cardiovascular mortality from 1990 to 2019. European Heart Journal, 41(1), 92-105.
65. Rudolph, A.E., et al. (2018). "Personalized Approaches for Heart Failure Management." Nature Reviews Cardiology, 15(8), 490-505.
66. Sarkar, D., et al. (2023). Structured exercise programs for patients with heart failure with preserved ejection fraction: A systematic review and meta-analysis. Cardiology in Review, 31(1), 40-47.
67. Schrijvers, G.F., et al. (2006). "Angiogenesis in Chronic Heart Failure: Potential Targets for Therapeutic Interventions." Heart Failure Reviews, 11(1), 13-22.
68. Schwingshackl, L., et al. (2018). "The Effects of Dietary Interventions on Heart Failure: A Systematic Review." Nutrition Reviews, 76(3), 212-228.
69. Smith, R. H., et al. (2021). Sacubitril/valsartan: A novel approach to calcium modulation in heart failure therapy. Cardiovascular Drugs and Therapy, 35(3), 291-299.
70. SOLVD Investigators. (1991). "Effect of Enalapril on Survival in Patients with Reducing Left Ventricular Dysfunction." New England Journal of Medicine, 325(5), 293-302.
71. Sud, M., et al. (2019). Epidemiology of heart failure: a global perspective. Nature Reviews Cardiology, 16(6), 367-379.
72. Verdasco, J. I., et al.. (2021). Efficacy of vasodilators in chronic heart failure with preserved ejection fraction: A meta-analysis of randomised controlled trials. Journal of Cardiovascular Pharmacology and Therapeutics, 26(2), 95-105.
73. Virani, S. S., et al. (2020). "Heart Disease and Stroke Statistics—2020 Update: A Report from the American Heart Association." Circulation, 141(9), e139-e596.
74. Wellens, H. J. J., et al. (2014). Atrial fibrillation: A global perspective. European Heart Journal, 35(17), 2283-2291.
75. Willey, J. Z., et al. (2021). "Shared Decision-Making in Heart Failure Management: A Systematic Review." Heart Failure Reviews, 26(1), 63-73.
76. Williams, B. C., et al. (2022). Assessing exercise capacity improvement in heart failure patients treated with Sacubitril/valsartan. *Journal of Physical Therapy Science*, 34(7), 457-465.
77. Yamamoto, S., et al. (2019). "Effect of Tai Chi on Exercise Capacity in Cognitive Function in Older Patients with Heart Failure: A Randomized Controlled Trial." Journal of Cardiology, 73(3), 231-238.
78. Yancy, C. W., et al. (2013). "2013 ACCF/AHA Guideline for the Management of Heart Failure." Journal of the American College of Cardiology, 62(16), e147- e239.
79. Zhang, X., et al.. (2021). "The impact of age and sex on heart failure phenotypes." Journal of the American College of Cardiology, 78(15), 1500-1513.
80. Zhang, Y., et al.. (2022). Advances in PET imaging of myocardial perfusion: Clinical implications for heart failure. Journal of Nuclear Cardiology, 29(3), 823-834.
81. Zile, M. R., et al. (2011). Management of heart failure with preserved ejection fraction.The American Journal of Medicine, 124(5), 401-408.
82. Zinman, B., et al. (2015). Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine, 373(22), 2117-2128.

Entered 20.03.2025