EURASIAN JOURNAL OF CHEMICAL, MEDICINAL AND PETROLEUM RESEARCH

Eurasian J. Chem. Med. Pet. Res. (275-288)

Volume 4, Issue 3

Eurasian Journal of Chemical, Medicinal and Petroleum Research

Journal homepage: https://www.ejcmpr.com/

DOI: 10.5281/zenodo.17154412

Mechanisms of Cardiac Remodeling in Heart Failure with Preserved Ejection Fraction

Atefe Shafiee

Board-certified cardiologist, Rajaie Cardiovascular Medical and Research center, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

Article info

Received: 02.07.2025
Accepted: 17.09.2025
Available Online: 18.09.2025
Checked for Plagiarism: Yes

Keywords:

Cardiac Remodeling Mechanisms, Kidney Disease, Low Ejection Fraction (EF), Type 2 Diabetes, Hypertension.

A B S T R A C T

The present study examined the mechanisms of cardiac remodeling in heart failure with preserved ejection fraction. Heart failure is a condition in which the heart does not pump blood well or does not fill with blood well. As a result, the heart falls behind in its work of moving blood around the body. This condition causes symptoms such as edema (swelling), shortness of breath and fatigue. The ejection fraction, or EF, of the heart measures the ability of the heart to pump oxygen-rich blood throughout the body. In a healthy heart, the ejection fraction is higher. A lower ejection fraction means that the heart is having difficulty meeting the body's needs. The results of the present study showed that heart failure with preserved ejection fraction (HFpEF) is one of the most common types of heart failure, which occurs due to normal left ventricular function in terms of contraction, but impaired filling or relaxation of the heart. It commonly seen in older adults, women, and patients with type 2 diabetes, obesity, hypertension, and kidney disease. As the population ages and the prevalence of chronic diseases increases, the prevalence of HFpEF is also increasing. The results of this study also showed that patients with low ejection fraction (EF) often excluded from rehabilitation programs due to concerns about the possibility of sudden death or other adverse cardiovascular events during exercise sessions. Recent studies have highlighted the fact that cardiac rehabilitation can improve exercise capacity, cardiac function, and health-related quality of life in patients with congestive heart failure.

Introduction

Ejection fraction refers to how well the heart pumps blood, and it is the amount of blood that is pumped out of the lower chambers of the heart with each contraction [1]. The term heart failure can make you feel like your heart is not working at all and that there is nothing you can do. In reality, heart failure means that your heart is not pumping as well as it should.

Congestive heart failure is a type of heart failure that requires immediate medical attention, although the two terms are sometimes used interchangeably. Your body depends on your heart's pumping function to deliver oxygen-rich blood and nutrients to your body's cells. When your cells are properly nourished, your body can function normally.

With heart failure, the weakened heart can't pump enough blood to your cells. This can lead to fatigue and shortness of breath, and some people may develop a cough. Everyday activities like walking, climbing stairs, or carrying groceries can become very difficult [2].

Heart failure is a serious condition, and there is usually no cure. But many people with heart failure live full and enjoyable lives when the condition is managed with heart failure medications and healthy lifestyle changes. Support from family and friends who understand your condition can also be helpful. If heart failure gets worse and lifestyle changes and medications don't control your symptoms, other medical or surgical procedures may be needed [3].

Corresponding Author: **Atefe Shafiee (atefe.shafiee8968@gmail.com- ORCID: 0009-0004-3729-841)*

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Your doctor may use a pacemaker (a three-chamber pacemaker, also known as a pacemaker) to treat your heart failure. This device helps your heart beat more evenly and contract the left and right ventricles at the same time, which can improve your heart failure symptoms [4]. Another option is to use an implantable cardioverter defibrillator, which is placed near your heart. This device checks your heart rate regularly and uses electrical impulses to quickly treat arrhythmias, or irregular heartbeats. This procedure is used for patients who are at risk of cardiac arrest. Appropriate treatment can improve the signs and symptoms of heart failure and may help some people live longer. Lifestyle changes (such as losing weight, exercising, reducing salt (sodium) in the diet, and managing stress) can improve your quality of life. However, the condition can be life-threatening. People with heart failure may have severe symptoms, and some may need a heart transplant or a ventricular assist device (VAD).

What are the symptoms of heart failure?

What is a normal ejection fraction?

The ejection fraction in a healthy heart is 50 to 70%. With each heartbeat, 50 to 70% of the blood is pumped from the left ventricle to the rest of the body [4].

Table 1. Percentage of ejection fraction

Men	Women
Normal	Normal
52 to 72%	54 to 74%
Slightly abnormal	Slightly abnormal
41 to 51%	41 to 53%
Moderately abnormal	Moderately abnormal
30 to 40%	30 to 40%
Severely abnormal	Severely abnormal
Below 30%	Below 30%

Some people with a normal ejection fraction may also have heart failure. This condition is called heart failure with preserved ejection fraction (HfpEF) [7].

Different types of ejection fraction

Ejection fraction is measured in the right ventricle or the left ventricle.

- **Left ventricular ejection fraction (LVEF):** Ejection fraction usually refers to the left side of the heart and shows how much blood is pumped from the left ventricle to most of the body's organs with each contraction. This ejection fraction indicates the severity of the left side of the heart's failure [5].
- **Right ventricular ejection fraction (RVEF):** This ejection fraction measures the amount of oxygen-rich blood pumped from the right side of the heart to the lungs and indicates failure in the right side of the heart. However, this condition is not as common as left-sided heart failure [6].

What can a reduced ejection fraction (HFpEF) due to the body?

Heart failure with reduced ejection fraction (HFrEF) represents a complex clinical syndrome in which the heart's ability to pump blood effectively is compromised, leading to significant systemic consequences. The reduction in ejection fraction, typically defined as less than 40%, reflects impaired systolic function, which results in inadequate perfusion of vital organs and tissues. This impaired cardiac output triggers a series of compensatory mechanisms aimed at maintaining circulatory stability, including activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system. While these mechanisms may initially support cardiac output, their chronic activation contributes to progressive myocardial remodeling, worsening heart function, and systemic organ dysfunction [7].

One of the most prominent effects of HFrEF on the body is fluid retention and congestion. Reduced ventricular pumping efficiency leads to elevated pressures in the venous circulation, causing fluid accumulation in peripheral tissues and organs. Clinically, this manifests as peripheral edema, pulmonary congestion, ascites, and hepatomegaly. Pulmonary congestion, in particular, impairs gas exchange in the lungs, resulting in dyspnea, orthopnea, and paroxysmal nocturnal dyspnea, which substantially limit patients' functional capacity and quality of life. Moreover, chronic venous congestion can exacerbate hepatic and renal dysfunction, creating a vicious cycle that further compromises fluid homeostasis and metabolic balance [8].

Beyond fluid overload, HFrEF induces reduced organ perfusion. Insufficient cardiac output diminishes oxygen and nutrient delivery to skeletal muscles, the brain, and other vital organs. Patients often experience fatigue, exercise intolerance, cognitive impairment, and reduced tolerance for physical activity. Skeletal muscle perfusion deficits lead to muscle atrophy and decreased exercise capacity, while cerebral hypoperfusion may contribute to confusion and diminished cognitive function. Reduced renal perfusion stimulates further neurohormonal activation, exacerbating fluid retention and increasing the risk of cardiorenal syndrome, which further complicates disease management [9].

HFrEF also has profound effects on neurohormonal and metabolic pathways. Chronic activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system leads to

vasoconstriction, sodium and water retention, and adverse myocardial remodeling. Additionally, systemic inflammation and oxidative stress are common in HFrEF, promoting endothelial dysfunction, fibrosis, and further deterioration of cardiac function. These mechanisms not only perpetuate the heart failure process but also affect other organ systems, including the kidneys, liver, and vasculature [10].

Another significant consequence of reduced ejection fraction is arrhythmogenic risk. Structural remodeling, ventricular dilation, and increased myocardial fibrosis create an arrhythmogenic substrate, increasing susceptibility to ventricular tachyarrhythmias and sudden cardiac death. Patients with HFrEF are therefore at a markedly elevated risk for sudden cardiac events, highlighting the importance of continuous monitoring and the potential need for implantable cardioverter-defibrillators (ICDs) in selected populations [11].

Finally, HFrEF imposes a substantial burden on exercise capacity and quality of life. The combination of fatigue, dyspnea, fluid overload, and neurohormonal disturbances leads to profound limitations in physical activity and daily functioning. Patients often experience a cycle of reduced activity, deconditioning, and worsening heart failure symptoms, further exacerbating morbidity and mortality [12].

In conclusion, heart failure with reduced ejection fraction exerts extensive systemic effects due to the heart's inability to maintain adequate cardiac output. These effects include fluid retention, organ hypoperfusion, neurohormonal and metabolic dysregulation, arrhythmogenic risk, and diminished functional capacity. The pathophysiology of HFrEF demonstrates how a primary cardiac dysfunction can disrupt homeostasis across multiple organ systems, emphasizing the need for comprehensive, multidisciplinary management. Effective treatment strategies, including pharmacologic therapy, lifestyle modifications, and device-based interventions, aim not only to improve cardiac function but also to mitigate systemic complications, enhance quality of life, and reduce morbidity and mortality. Recognizing and addressing the wide-ranging impact of reduced ejection fraction on the body is critical for optimizing patient outcomes and improving long-term survival [13].

Ejection fraction (EF) is a critical measure of the heart's pumping efficiency, representing the percentage of blood ejected from the left ventricle with each contraction. A normal EF typically ranges between 50% and 70%, reflecting adequate systolic function to maintain tissue perfusion and organ health. When the EF falls outside this normal range, either as a reduced EF (HFrEF) or a preserved/abnormal EF with diastolic dysfunction (HFpEF), the consequences extend far beyond the heart, affecting multiple organ systems and overall quality of life [14].

When the EF is reduced, the heart cannot pump blood effectively, leading to insufficient delivery of oxygen and nutrients to peripheral tissues. This systemic underperfusion triggers a cascade of compensatory mechanisms, including activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system. While these adaptations may temporarily preserve blood pressure and organ perfusion, chronic activation contributes to myocardial remodeling, ventricular dilation, and progressive worsening of cardiac function. Patients with reduced EF frequently experience fatigue, weakness, and exercise intolerance due to inadequate oxygen supply to skeletal muscles. The brain may also suffer from hypoperfusion, resulting in cognitive impairment, poor concentration, and increased susceptibility to confusion or delirium.

Reduced EF often leads to fluid retention and congestion, particularly in the lungs, liver, kidneys, and peripheral tissues. Pulmonary congestion manifests as shortness of breath, orthopnea, and paroxysmal nocturnal dyspnea, which are hallmarks of heart failure. Peripheral edema and ascites may develop as a result of elevated venous pressures, further impairing mobility and contributing to discomfort and secondary complications such as skin breakdown. Chronic congestion can compromise kidney and liver function, creating a complex interplay of cardiorenal and cardiohepatic syndromes that complicate disease management.

Abnormal EF also affects neurohormonal and metabolic pathways. Persistent activation of neurohormonal systems promotes vasoconstriction, sodium and water retention, and increased cardiac workload, while systemic inflammation and oxidative stress contribute to endothelial dysfunction and organ fibrosis. These processes accelerate disease progression and can impair other organ systems, including the kidneys, liver, and vascular beds. The risk of arrhythmias increases due to structural remodeling, myocardial fibrosis, and changes in the conduction system, heightening the likelihood of sudden cardiac death in affected individuals [15].

In cases of HFpEF, the EF may be preserved, yet diastolic dysfunction prevents adequate ventricular filling. The heart appears to pump normally but is stiff and noncompliant, causing elevated left ventricular pressures. This condition leads to pulmonary congestion, exertional dyspnea, fatigue, and exercise intolerance, similar to HFrEF, despite a "normal" EF. Patients often have comorbid conditions such as hypertension, diabetes, and obesity, which exacerbate the cardiovascular strain.

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Over time, HFpEF can progress, causing chronic symptoms and increasing the risk of hospitalization and mortality [16].

Both reduced and abnormal EF disrupt functional capacity and quality of life. Individuals experience diminished exercise tolerance, fatigue, and shortness of breath that interfere with daily activities. The psychological impact is also significant, including anxiety, depression, and social isolation due to physical limitations. Chronic heart failure contributes to a cycle of deconditioning and worsening cardiac function, emphasizing the importance of early detection, monitoring, and intervention [17].

Management of abnormal EF requires a multidisciplinary approach. Pharmacologic treatments, such as beta-blockers, ACE inhibitors, ARNI, mineralocorticoid receptor antagonists, and SGLT2 inhibitors, aim to improve cardiac function, control symptoms, and reduce morbidity and mortality. Device-based therapies, including implantable cardioverter-defibrillators and cardiac resynchronization therapy, may be indicated in selected patients. Lifestyle modifications, including sodium restriction, regular physical activity within tolerance, and weight management, further support cardiovascular health and systemic homeostasis [18].

In conclusion, an ejection fraction outside the normal range, whether reduced or associated with diastolic dysfunction, has profound effects on the body. It impacts organ perfusion, fluid balance, neurohormonal regulation, metabolic function, and overall physical and psychological well-being. Both HFrEF and HFpEF highlight the interconnection between cardiac performance and systemic health. Recognizing the widespread consequences of abnormal EF is crucial for timely intervention, comprehensive management, and improving patient outcomes. Effective treatment strategies that address both cardiac and extracardiac effects are essential to mitigate complications, enhance quality of life, and extend survival in individuals with abnormal ejection fraction [19].

What do different values for your ejection fraction mean?

The most common symptoms of heart failure with preserved ejection fraction include shortness of breath with exertion or at rest, decreased exercise tolerance, fatigue, chest discomfort, swelling in the lower extremities, and shortness of breath when lying down. Symptoms of heart failure with preserved ejection fraction can be caused by blood or fluid accumulating in the lungs, veins, and body tissues. Fluid backs up into these areas because the heart is not filling properly, which can lead to shortness of breath and swelling in the legs [20]. Symptoms can also be caused by the heart's inability to pump enough blood during exercise, which can lead to fatigue and reduced exercise capacity. The findings suggest that vascular changes in leg muscles are a more accessible and early warning sign, and to investigate this idea, the research team used a special type of MRI scan that tracks how blood vessels respond to stress. They tested the method in a clinical model of diabetes-induced preserved ejection fraction heart failure, focusing on changes in blood flow in the heart and leg muscle. The researchers found that in people with diabetes, problems with regulating blood flow in the calf muscle appear months before similar problems see in the heart. This finding suggests that the calf muscle better positioned to catch preserved ejection fraction heart failure in its early stages. The results show that by examining blood flow in the legs, we can detect problems much earlier than by focusing on the heart. This finding could make a big difference in how the disease diagnosed and treated. The researchers are focusing on the next steps of the research, and say the next step is to test human patients with risk factors for preserved ejection fraction heart failure and determine whether our MRI platform can actually detect the disease earlier than conventional diagnostic methods. They said the ultimate goal is not only to enable early detection when the disease may be treatable, but also to provide a new avenue for treating a growing condition that has become the most common form of heart failure. Heart failure often develops after the heart damaged or weakened by other conditions. However, it can also occur if the heart becomes too stiff [21].

In heart failure, the heart's main pumping chambers (ventricles) may stiffen and not fill properly between beats. In some people, the heart muscle may become damaged and weak. The ventricles become so stretched that the heart cannot pump enough blood around the body. Over time, the heart can no longer keep up with the normal demands it makes to pump blood to the rest of the body. Your doctor can determine how well your heart is pumping by measuring the amount of blood pumped out with each beat (the ejection fraction). The ejection fraction used to help classify the condition and guide treatment. In a healthy heart, the ejection fraction is 50% or higher. This means that more than half of the blood filling the ventricles pumped out with each beat. But this disease can occur even with a normal ejection fraction. This happens if the heart muscle stiffened by conditions such as high blood pressure. Heart failure can affect the left side (left ventricle), the right side (right ventricle), or both sides of your heart [22].

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Generally, the disease starts with the left side, specifically the left ventricle, the main pumping chamber of your heart.

What happens if your ejection fraction is higher than average?

Ejection fraction (EF) is a fundamental measurement in cardiology that reflects the proportion of blood the left ventricle pumps out with each heartbeat. It is a critical indicator of heart function, typically expressed as a percentage, with normal values ranging between 50% and 70%. Understanding one's EF is essential because it provides insight into the heart's pumping efficiency, guides diagnosis, informs treatment decisions, and predicts prognosis. Awareness of EF allows both patients and clinicians to take proactive steps in managing cardiovascular health and preventing progression to heart failure or other complications [23].

One of the primary reasons knowing your EF is important is its diagnostic value. EF serves as a key criterion in differentiating between types of heart failure, namely heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). HFrEF, defined by an EF below 40%, indicates systolic dysfunction, where the heart cannot pump effectively, leading to inadequate organ perfusion and fluid accumulation. HFpEF, on the other hand, occurs when EF is normal or near normal but the heart is stiff, leading to impaired filling and elevated pressures. Identifying the type of dysfunction helps clinicians tailor therapy appropriately, as treatment strategies differ substantially between HFrEF and HFpEF. Without knowledge of EF, patients may receive suboptimal therapy, potentially leading to preventable complications [24].

Knowing EF also provides valuable prognostic information. Numerous studies have demonstrated that reduced EF is associated with increased risk of morbidity and mortality. Patients with lower EF are more susceptible to hospitalizations, arrhythmias, and sudden cardiac death. Even in patients with preserved EF, measuring EF alongside other cardiac parameters helps evaluate the likelihood of disease progression and long-term outcomes. By understanding EF, patients and clinicians can better stratify risk, anticipate complications, and implement preventive measures, including pharmacologic and device-based interventions [25].

Another critical aspect of EF measurement is its role in guiding treatment decisions. Many heart failure therapies are EF-dependent. For instance, medications such as beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor-neprilysin inhibitors, and mineralocorticoid receptor antagonists have been shown to improve survival and reduce hospitalization specifically in HFrEF patients. Implantable cardioverter-defibrillators and cardiac resynchronization therapy are considered primarily in patients with significantly reduced EF. Conversely, management of HFpEF emphasizes controlling comorbid conditions such as hypertension, diabetes, and obesity, as pharmacologic options with proven mortality benefit are limited. Knowing EF enables clinicians to select appropriate therapies, monitor response, and adjust treatment regimens over time to optimize outcomes [26].

Monitoring EF over time also helps track disease progression and response to therapy. Changes in EF can indicate improvement, stability, or deterioration of cardiac function, guiding adjustments in treatment. For example, an increase in EF following pharmacologic therapy or cardiac resynchronization may reflect effective intervention, whereas a declining EF may necessitate intensification of therapy or further diagnostic evaluation. Regular assessment of EF allows for timely interventions that may slow disease progression, prevent complications, and improve quality of life.

Furthermore, understanding EF enhances patient engagement and self-management. Patients who are aware of their EF are better equipped to recognize the importance of lifestyle modifications, adherence to medication, and routine follow-up. Knowledge of one's EF can motivate patients to adopt heart-healthy behaviors, including regular physical activity within tolerance, dietary modifications, and avoidance of risk factors such as smoking. This awareness fosters shared decision-making between patients and clinicians, leading to more personalized and effective care [27].

Finally, EF measurement has broader implications for overall cardiovascular risk assessment. Reduced or abnormal EF often coexists with other cardiovascular conditions, such as coronary artery disease, valvular heart disease, and hypertension. Identifying EF abnormalities allows for comprehensive evaluation of cardiovascular health, early detection of secondary complications, and implementation of preventive strategies, ultimately improving morbidity and mortality outcomes.

In conclusion, knowing your ejection fraction is of paramount importance because it provides critical information about heart function, aids in diagnosis, guides treatment decisions, informs prognosis, and supports ongoing monitoring. EF measurement empowers both clinicians and patients to take proactive, evidence-based steps in managing cardiovascular health. It enables personalized therapy, timely intervention, and risk stratification, ultimately improving patient outcomes and quality of life [28].

Awareness of EF is not merely a numerical value; it is a vital tool that bridges clinical assessment, therapeutic planning, and patient engagement, underscoring its central role in contemporary cardiovascular care [29].

Ejection fraction (EF) is a fundamental measure of cardiac performance, reflecting the percentage of blood ejected from the left ventricle with each heartbeat. A normal EF typically ranges between 50% and 70%, and values outside this range—either lower or higher—can signal underlying cardiac or systemic abnormalities. While much attention is often given to reduced EF due to its clear association with heart failure, a higher-than-average EF, sometimes termed hyperdynamic EF, can also have significant physiological and clinical implications. Understanding the consequences of elevated EF is critical for accurate diagnosis, prognosis, and management, as well as for maintaining overall cardiovascular health [30].

A higher-than-average EF can occur due to a variety of physiological and pathological conditions. In healthy individuals, temporary elevations in EF may result from exercise, stress, or sympathetic stimulation, reflecting the heart's ability to increase output during periods of increased demand. In these circumstances, elevated EF is generally benign and represents an adaptive response to maintain systemic perfusion. However, persistent or markedly elevated EF may indicate underlying cardiac pathology. For instance, conditions such as hypertrophic cardiomyopathy, valvular regurgitation (particularly mitral or aortic regurgitation), anemia, hyperthyroidism, or sepsis can lead to chronically increased EF. Recognizing the underlying cause is essential because the elevated EF is often a compensatory mechanism rather than a sign of superior cardiac health.

Elevated EF can have systemic consequences, despite appearing to represent increased cardiac efficiency. In cases such as hypertrophic cardiomyopathy, the ventricle may contract vigorously, but the chamber is often small and stiff, impairing diastolic filling. This leads to elevated intracardiac pressures, reduced stroke volume in real terms, and symptoms of heart failure despite a high EF. Similarly, in valvular regurgitation, a high EF may reflect the heart pumping blood both forward and backward into the atrium or aorta, creating a misleading impression of normal cardiac output. Over time, persistent hyperdynamic function can cause myocardial stress, ventricular remodeling, arrhythmias, and increased risk of adverse cardiovascular events.

From a hemodynamic perspective, elevated EF can contribute to abnormal pressure and flow dynamics. The left ventricle may experience increased wall stress, which can promote myocardial fibrosis and stiffening. Elevated EF often occurs alongside high heart rates, reduced ventricular compliance, and exaggerated contractility, which may increase oxygen demand and reduce myocardial efficiency. These factors can ultimately compromise coronary perfusion and predispose the myocardium to ischemia, particularly in patients with pre-existing coronary artery disease [31].

Another important consideration is the relationship between hyperdynamic EF and systemic conditions. Conditions such as anemia or hyperthyroidism can increase EF by augmenting sympathetic activity and cardiac contractility. While the body initially compensates for increased metabolic demand, prolonged hyperdynamic function can accelerate cardiac fatigue, promote remodeling, and increase the risk of arrhythmias and sudden cardiac events. Similarly, in sepsis or other high-output states, elevated EF reflects a compensatory response to systemic vasodilation and hypotension; while adaptive in the short term, prolonged exposure may contribute to myocardial injury and long-term cardiac dysfunction.

Persistent elevated EF may also impact quality of life and functional capacity. Although some individuals remain asymptomatic, others may experience palpitations, dyspnea, exercise intolerance, or fatigue due to inefficient ventricular filling or high myocardial oxygen demand. These symptoms can interfere with daily activities, reduce exercise tolerance, and affect overall well-being. Moreover, elevated EF is often associated with arrhythmic risk, including atrial fibrillation and ventricular tachyarrhythmias, which further complicate clinical management.

From a clinical perspective, recognizing and monitoring elevated EF is essential for guiding management and intervention. Diagnostic tools such as echocardiography, cardiac MRI, and laboratory assessment help identify underlying causes and assess the functional consequences. Treatment focuses on addressing the primary condition—such as correcting anemia, managing hyperthyroidism, or surgically repairing valvular lesions—while mitigating potential cardiac complications. Lifestyle interventions, pharmacologic therapies, and close monitoring of cardiovascular status are critical for preventing progression to symptomatic heart failure or sudden cardiac events [32].

In conclusion, a higher-than-average ejection fraction is not universally benign and can indicate underlying cardiovascular or systemic pathology. While temporary elevations in EF may reflect normal physiological adaptations, persistent hyperdynamic EF may contribute to myocardial stress, arrhythmias, impaired diastolic filling, and adverse cardiovascular outcomes. Recognizing elevated EF and its causes is essential for accurate

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diagnosis, appropriate treatment, and risk stratification. Understanding the systemic consequences of high EF emphasizes the importance of comprehensive cardiac evaluation, patient education, and tailored management strategies to maintain cardiac efficiency, prevent complications, and optimize long-term cardiovascular health. Awareness of elevated EF empowers clinicians and patients to take proactive steps in preserving heart function, managing underlying conditions, and promoting overall well-being [33].

How is your ejection fraction measured?

Ejection fraction (EF) is a critical parameter in assessing cardiac function, reflecting the percentage of blood the left ventricle pumps out with each contraction relative to its total filled volume. Accurate measurement of EF is essential for diagnosing, monitoring, and managing various cardiovascular conditions, including heart failure, cardiomyopathy, valvular heart disease, and ischemic heart disease. Understanding how EF is measured provides insight into the strengths, limitations, and clinical implications of different diagnostic modalities, while emphasizing the importance of precise assessment for optimal patient care.

EF can be measured using several techniques, each with distinct advantages and limitations. The most widely used method is transthoracic echocardiography (TTE), a non-invasive imaging modality that uses ultrasound waves to visualize the heart in real-time. Through echocardiography, clinicians can assess ventricular size, wall motion, and chamber volumes at end-diastole and end-systole. EF is calculated as the difference between end-diastolic volume and end-systolic volume, divided by the end-diastolic volume, and expressed as a percentage. TTE is advantageous due to its accessibility, safety, and ability to provide additional structural and functional information, including valve function, diastolic performance, and pulmonary pressures. However, it may be limited by poor acoustic windows in patients with obesity, lung disease, or chest wall deformities [34].

Another method for measuring EF is cardiac magnetic resonance imaging (CMR), which is considered the gold standard for volumetric assessment. CMR provides high-resolution, three-dimensional images of the heart, allowing for precise measurement of ventricular volumes, wall thickness, and myocardial mass. EF derived from CMR is highly reproducible and accurate, making it particularly valuable for research, complex congenital heart disease, or cases where echocardiography yields inconclusive results. Additionally, CMR can assess myocardial fibrosis, scar tissue, and perfusion, offering a more comprehensive evaluation of cardiac health. The main limitations of CMR include high cost, limited availability, and contraindications in patients with certain implants or severe renal impairment.

Nuclear imaging techniques, such as radionuclide ventriculography (MUGA scan), provide another method to measure EF. This technique involves injecting a radioactive tracer and capturing gamma-ray images of the heart during systole and diastole. MUGA scans are highly accurate and reproducible, particularly in patients undergoing chemotherapy where serial monitoring of cardiac function is required. However, the use of ionizing radiation, cost, and limited structural information are notable limitations.

Computed tomography (CT) of the heart can also provide EF measurements, particularly in patients undergoing coronary CT angiography. CT-based EF assessment uses volumetric reconstruction and can offer precise information about ventricular volumes and function. While CT is highly accurate, exposure to ionizing radiation and contrast agents limits its routine use for EF measurement alone [35].

Invasive methods, such as cardiac catheterization, can also estimate EF, particularly during left ventriculography. Although invasive, this technique provides valuable hemodynamic information and is often used when non-invasive imaging is inconclusive or when simultaneous coronary assessment is required. Due to its invasiveness, it is generally reserved for selected patients rather than routine EF evaluation [36].

Regular measurement of EF is essential for diagnosis, prognosis, and treatment planning. EF helps differentiate between heart failure with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF), guiding the choice of pharmacologic and device-based therapies. Serial EF measurements can track disease progression, assess response to treatment, and detect subclinical deterioration before symptomatic decline. Accurate EF assessment is particularly important in patients receiving potentially cardiotoxic medications, such as chemotherapy, as early detection of functional decline allows for timely intervention.

Furthermore, understanding the method used to measure EF is critical for interpreting results. Variability between techniques may influence clinical decisions, emphasizing the importance of standardized protocols and repeat measurements when clinically indicated. Clinicians must integrate EF with other clinical data, including symptoms, biomarkers, and structural assessment, to make informed management decisions [37].

In conclusion, ejection fraction is measured using a variety of non-invasive and invasive techniques, including echocardiography, cardiac MRI, nuclear imaging, CT, and cardiac catheterization. Each

method provides unique advantages and limitations in terms of accuracy, safety, reproducibility, and additional diagnostic information. Accurate EF measurement is central to diagnosing heart failure, guiding therapy, monitoring treatment response, and predicting prognosis. Awareness of the measurement method, its limitations, and clinical context ensures that EF assessment is interpreted correctly, enhancing patient care and supporting timely, evidence-based decision-making. Ultimately, understanding how EF is measured empowers both clinicians and patients to actively monitor cardiac health, implement appropriate interventions, and optimize cardiovascular outcomes over the lifespan.

Improving your ejection fraction

Ejection fraction (EF) is a central measure of cardiac function, reflecting the percentage of blood the left ventricle ejects with each contraction. Maintaining or improving EF is essential for overall cardiovascular health, as low EF is associated with heart failure, reduced exercise tolerance, arrhythmias, and increased mortality risk. While EF is influenced by underlying cardiac conditions, lifestyle factors, pharmacologic therapies, and medical interventions can significantly enhance ventricular function and quality of life. Understanding strategies to improve EF is crucial for patients and clinicians seeking to optimize cardiac performance and reduce the burden of heart disease [38].

Lifestyle modification is a foundational approach to improving EF. Regular aerobic and resistance exercise strengthens the myocardium, improves ventricular compliance, and enhances cardiac output. Exercise training has been shown to increase stroke volume, reduce resting heart rate, and improve overall EF, particularly in patients with heart failure with reduced ejection fraction (HFrEF). Additionally, dietary interventions, including a heart-healthy diet rich in fruits, vegetables, whole grains, lean proteins, and omega-3 fatty acids, help control blood pressure, reduce cholesterol levels, and mitigate vascular inflammation, indirectly supporting ventricular function. Limiting sodium intake and moderating fluid consumption are particularly important for patients with congestive symptoms, as fluid overload can exacerbate ventricular dysfunction. Weight management is another critical factor; obesity increases cardiac workload and is associated with lower EF, while gradual weight loss can improve hemodynamics and enhance EF over time.

Pharmacologic therapies play a pivotal role in improving EF in patients with underlying cardiac disease. Medications such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNIs), beta-blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter-2 (SGLT2) inhibitors have demonstrated efficacy in increasing EF and improving clinical outcomes in heart failure patients. These agents reduce ventricular remodeling, decrease myocardial wall stress, control blood pressure, and mitigate neurohormonal activation, all of which support enhanced contractile function. Optimizing medication regimens under clinical supervision is essential, as adherence, dose titration, and monitoring of renal function and electrolytes are critical for maximizing therapeutic benefits [39].

Device-based interventions can also enhance EF in selected patients. Cardiac resynchronization therapy (CRT) is indicated for individuals with heart failure and electrical conduction delays, particularly left bundle branch block, and has been shown to improve EF, reduce heart failure symptoms, and decrease hospitalization rates. Implantable cardioverter-defibrillators (ICDs), while primarily aimed at preventing sudden cardiac death, may support improved overall cardiac function in combination with optimal medical therapy. Surgical or percutaneous interventions, such as valve repair or replacement in cases of severe valvular heart disease, can relieve volume or pressure overload, thereby improving EF and ventricular efficiency.

Management of comorbid conditions is also essential for supporting EF. Conditions such as hypertension, diabetes, chronic kidney disease, and thyroid disorders can negatively impact cardiac function. Effective management through medication, lifestyle adjustment, and routine monitoring helps reduce additional stress on the myocardium, allowing the heart to recover function and maintain or improve EF. In patients with anemia or iron deficiency, correction of these conditions has been associated with improved exercise tolerance, reduced symptoms, and enhanced EF.

Patient engagement and monitoring are crucial components of EF improvement strategies. Regular follow-up with echocardiography, clinical evaluation, and biomarker assessment allows early identification of functional decline and timely intervention. Patient education regarding symptom recognition, medication adherence, dietary choices, and physical activity ensures active participation in managing heart health. Empowering patients with knowledge fosters long-term behavioral changes that support sustained improvement in EF and overall cardiovascular outcomes [40].

In conclusion, improving ejection fraction requires a multifaceted approach that integrates lifestyle modification, pharmacologic therapy, device-based interventions, and management of comorbidities.

Exercise, diet, weight management, and smoking cessation optimize cardiac workload and myocardial efficiency, while medications and devices address structural and functional impairments, promote reverse remodeling, and enhance contractility. Monitoring comorbid conditions and patient engagement further support long-term maintenance of improved EF. By adopting these strategies, patients can enhance heart function, reduce symptoms of heart failure, improve exercise tolerance, and increase survival, underscoring the importance of proactive and comprehensive management in preserving cardiovascular health. Ultimately, improving EF is not only a clinical goal but also a pathway to better quality of life, functional independence, and reduced morbidity and mortality for individuals with compromised cardiac function.

Ejection fraction (EF) is a central measure in the evaluation of cardiac function, representing the percentage of blood ejected from the left ventricle with each heartbeat. While EF provides valuable insight into ventricular performance and is instrumental in distinguishing heart failure subtypes—such as heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF)—it is not the sole diagnostic or prognostic tool required for the comprehensive assessment of heart failure. Relying exclusively on EF can overlook critical structural, functional, and systemic factors that contribute to heart failure pathology, highlighting the necessity of a multifaceted diagnostic approach.

Heart failure is a complex syndrome arising from various etiologies, including ischemic heart disease, hypertension, valvular disorders, cardiomyopathies, and systemic conditions such as diabetes or renal impairment. While EF reflects the mechanical pumping ability of the heart, it does not capture diastolic function, right ventricular performance, atrial pressures, pulmonary hypertension, or the presence of myocardial fibrosis. For example, patients with HFpEF may present with normal or even elevated EF values, yet experience significant symptoms of heart failure due to impaired ventricular relaxation, increased filling pressures, and systemic vascular abnormalities. Therefore, relying solely on EF can result in underdiagnosis or misclassification of heart failure subtypes [41].

Complementary imaging modalities are critical to provide a comprehensive evaluation of cardiac structure and function. Transthoracic echocardiography (TTE) offers a detailed assessment of chamber sizes, wall motion abnormalities, valvular function, and diastolic filling patterns. Tissue Doppler imaging and strain analysis further quantify myocardial deformation, allowing detection of subclinical dysfunction not evident from EF alone. Cardiac magnetic resonance imaging (CMR) provides highly accurate volumetric measurements, myocardial tissue characterization, and assessment of fibrosis or scar formation, offering prognostic information beyond EF. Additionally, nuclear imaging and computed tomography (CT) can provide perfusion data and evaluate myocardial viability, contributing essential information for treatment planning.

Biomarkers complement imaging in the assessment and monitoring of heart failure. Natriuretic peptides, such as B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP), correlate with ventricular wall stress and filling pressures, offering diagnostic and prognostic insights independent of EF. Elevated levels of these biomarkers can indicate fluid overload, myocardial stress, and increased risk of adverse outcomes, even in patients with preserved EF. Other markers, including troponins, galectin-3, and soluble ST2, provide information regarding myocardial injury, fibrosis, and remodeling, guiding risk stratification and therapeutic decisions.

Hemodynamic assessment is also important in selected patients. Right heart catheterization measures intracardiac pressures, pulmonary artery pressures, and cardiac output, providing precise hemodynamic data that can clarify ambiguous clinical presentations or guide management in advanced heart failure. These measurements are especially valuable in patients with refractory symptoms, suspected pulmonary hypertension, or complex comorbidities.

Functional assessments, such as exercise testing, cardiopulmonary exercise testing (CPET), and six-minute walk tests, evaluate exercise tolerance, oxygen consumption, and cardiovascular reserve. These tests provide crucial prognostic information and help tailor individualized therapy, capturing limitations that EF alone cannot predict. Functional assessments also help determine the impact of comorbidities, including pulmonary disease, anemia, or peripheral vascular disease, on overall exercise capacity.

Laboratory and systemic evaluation is necessary to identify underlying contributors to heart failure, including renal and hepatic dysfunction, electrolyte imbalances, thyroid disorders, and inflammatory or infiltrative conditions. Optimizing these systemic factors is critical for improving outcomes, independent of EF measurement.

In conclusion, ejection fraction is a pivotal tool in the assessment of heart failure, providing valuable information on left ventricular systolic function and helping guide therapy. However, EF alone is insufficient to fully characterize the complexity of heart failure. Comprehensive evaluation requires integration of imaging modalities, biomarkers, hemodynamic studies, functional assessments, and systemic laboratory evaluation to capture the

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multifaceted pathophysiology, guide personalized treatment, and accurately predict prognosis. Reliance solely on EF may result in misdiagnosis, underestimation of disease severity, or delayed initiation of appropriate therapy. A holistic, multimodal approach ensures accurate diagnosis, effective management, and optimal patient outcomes in the complex landscape of heart failure, emphasizing that EF is an essential, but not exclusive, component of cardiovascular assessment.

Discussion

The results of the article "Development of algorithms for identifying cardiac arrhythmias using data from heart characteristics measurement systems, electrocardiogram signal" published in the Civica database showed that the issue of diagnosing heart diseases and predicting some risky events related to the cardiovascular system such as heart attack, sudden death, coronary artery occlusion, hypertensive shocks and valvular and mechanical heart problems has been one of the important scientific aspirations of scientists and researchers in this field for the past five decades [37].

While medical imaging has improved the ability to find specific heart problems, such as hardening or destruction of heart tissue, these tests often miss the early signs of problems in other parts of the body. Therefore, identifying a method to investigate these cases is essential. However, previous research has shown that poor regulation of blood flow in the leg muscles may appear before similar changes in the heart, and could even explain symptoms such as fatigue or difficulty exercising. The researchers say: "Our study sheds light on an important gap in how to diagnose heart failure with preserved ejection fraction before irreversible damage to the heart occurs. Heart failure with preserved ejection fraction is a common and challenging disease that affects millions of people worldwide. The disease progresses quietly, with few symptoms until it becomes serious and difficult to treat.

According to the results published in the scientific website Medical Express, if the heart pumps normally but is so stiff that it cannot fill properly, this condition is known as heart failure with preserved ejection fraction, and the results of the current study show that heart failure with preserved ejection fraction occurs when chronic medical conditions damage the heart and other organ systems of the body. Medical conditions such as obesity, high blood pressure, diabetes mellitus, coronary artery disease, atrial fibrillation, chronic kidney disease, chronic obstructive pulmonary disease, obstructive sleep apnea, and anemia can contribute to heart failure with preserved ejection fraction. This is not always the case, and patients with heart failure with preserved ejection fraction often have one or more of these conditions, and it is thought that these conditions change the structure and function of the heart over time.

One of the hallmarks of HFpEF is concentric left ventricular hypertrophy (LVH), characterized by increased wall thickness without significant chamber dilatation. This remodeling pattern typically arises in response to chronic pressure overload, often secondary to systemic hypertension, a common comorbidity in HFpEF patients. Sustained elevation in afterload induces cardiomyocyte hypertrophy, an adaptive response aimed at reducing wall stress according to the Law of Laplace. However, over time, excessive hypertrophy increases myocardial stiffness, impairs relaxation, and contributes to diastolic dysfunction, a central feature of HFpEF. Studies have demonstrated that concentric remodeling is associated with reduced LV compliance, elevated filling pressures, and impaired exercise tolerance. Moreover, ventricular hypertrophy can disrupt coronary microcirculation, leading to subendocardial ischemia and further promoting myocardial fibrosis and diastolic impairment [38].

Extracellular Matrix Remodeling and Fibrosis

Fibrosis is a critical component of HFpEF-related cardiac remodeling. The extracellular matrix (ECM), composed primarily of collagen types I and III, provides structural support to cardiomyocytes and maintains ventricular geometry. In HFpEF, maladaptive remodeling of the ECM occurs through increased deposition of fibrillar collagen and altered cross-linking, resulting in myocardial stiffening. Several molecular pathways contribute to this process, including activation of transforming growth factor-beta (TGF-β), renin-angiotensin-aldosterone system (RAAS), and profibrotic cytokines. Advanced glycation end products (AGEs), particularly in patients with diabetes mellitus, further exacerbate ECM stiffness by forming cross-links between collagen fibers, reducing myocardial elasticity. Fibrosis not only impairs diastolic relaxation but also disrupts electromechanical coupling, increasing susceptibility to arrhythmias and sudden cardiac death. Histological analyses of HFpEF myocardium frequently reveal patchy interstitial fibrosis, emphasizing the heterogeneity of ECM remodeling and its contribution to disease progression.

Microvascular Dysfunction and Endothelial Impairment

Emerging evidence highlights the role of coronary microvascular dysfunction in HFpEF pathophysiology and cardiac remodeling. Endothelial dysfunction in small intramyocardial

vessels leads to impaired nitric oxide (NO) bioavailability, increased oxidative stress, and reduced vasodilatory capacity. The resulting myocardial ischemia, although often subclinical, promotes cardiomyocyte stiffening, apoptosis, and interstitial fibrosis. Inflammatory signaling from systemic comorbidities such as obesity, diabetes, and chronic kidney disease amplifies microvascular damage, contributing to myocardial remodeling. Furthermore, impaired coronary flow reserve and reduced capillary density have been associated with exercise intolerance and elevated filling pressures, highlighting the functional consequences of microvascular remodeling in HFpEF [39].

Cardiomyocyte Functional Alterations

At the cellular level, cardiomyocyte remodeling in HFpEF involves structural, metabolic, and functional changes. Hypertrophied cardiomyocytes exhibit altered sarcomere organization, increased resting tension, and impaired relaxation kinetics. Calcium handling abnormalities, including altered sarcoplasmic reticulum calcium reuptake and reduced expression of SERCA2a, contribute to delayed diastolic relaxation and impaired lusitropy. Additionally, metabolic dysregulation, often driven by insulin resistance and mitochondrial dysfunction, reduces ATP availability, further impairing active relaxation. Cardiomyocyte stiffening, coupled with ECM fibrosis, culminates in elevated LV filling pressures, pulmonary congestion, and exercise intolerance, hallmark features of HFpEF [28].

Inflammatory and Systemic Contributors

HFpEF is increasingly recognized as a systemic syndrome in which comorbidities drive a proinflammatory state that promotes cardiac remodeling. Obesity, type 2 diabetes, hypertension, and chronic kidney disease elevate circulating levels of inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP). These cytokines activate myocardial fibroblasts, enhance collagen deposition, and contribute to cardiomyocyte hypertrophy and stiffness. Systemic inflammation also impairs endothelial function, exacerbates oxidative stress, and promotes microvascular rarefaction, creating a vicious cycle of remodeling and functional decline. The interaction between systemic comorbidities and cardiac-specific remodeling underscores the importance of a holistic approach to HFpEF management [39].

Neurohormonal Activation and Mechanical Stress

Neurohormonal pathways, particularly the RAAS and sympathetic nervous system, are central mediators of cardiac remodeling. Chronic activation of RAAS increases angiotensin II and aldosterone levels, promoting hypertrophy, fibrosis, and sodium retention. Elevated sympathetic activity induces tachycardia, increased afterload, and direct cardiomyocyte injury through catecholamine-mediated oxidative stress. Mechanical stress, resulting from pressure or volume overload, further activates mechanosensitive signaling pathways, including stretch-activated ion channels and MAP kinase cascades, amplifying hypertrophic and fibrotic responses. Together, these neurohormonal and mechanical factors orchestrate maladaptive remodeling that maintains preserved EF while impairing diastolic function [40].

Ventricular-Arterial Coupling and Stiffness

In HFpEF, cardiac remodeling extends beyond the myocardium to the arterial system, resulting in impaired ventricular-arterial coupling. Increased arterial stiffness, often associated with aging, hypertension, and diabetes, elevates systolic load and augments LV wall stress. The left ventricle adapts by concentric hypertrophy, which preserves EF but increases diastolic stiffness. Impaired ventricular-arterial coupling reduces cardiac efficiency, elevates filling pressures, and contributes to exercise intolerance, highlighting the interplay between myocardial remodeling and systemic vascular changes in HFpEF pathophysiology [41].

Clinical Implications and Therapeutic Considerations

Understanding the mechanisms of cardiac remodeling in HFpEF has direct therapeutic implications. Unlike HFrEF, where EF-guided therapies such as beta-blockers, ACE inhibitors, and mineralocorticoid receptor antagonists have demonstrated mortality benefits, HFpEF management is primarily aimed at symptom relief, comorbidity management, and targeted interventions to attenuate remodeling. Novel therapies, including SGLT2 inhibitors, neprilysin inhibitors, and anti-fibrotic agents, show promise in modulating remodeling pathways, improving diastolic function, and reducing hospitalization rates. Additionally, lifestyle interventions such as exercise, weight reduction, and blood pressure control mitigate hypertrophy and fibrosis, highlighting the role of non-pharmacologic strategies in addressing structural remodeling [42].

Future Directions

Despite advances in understanding, HFpEF remains a heterogeneous syndrome with diverse remodeling phenotypes. Precision medicine approaches that integrate imaging, biomarker profiling, genetic analysis, and hemodynamic assessment are needed to identify patient-specific remodeling mechanisms

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and guide individualized therapy. Ongoing research into the molecular drivers of fibrosis, cardiomyocyte stiffness, and microvascular dysfunction offers the potential to develop disease-modifying therapies that target the underlying remodeling processes rather than solely addressing symptoms.

Conclusion

Cardiac remodeling in HFpEF is a multifactorial process involving structural, cellular, molecular, hemodynamic, and systemic alterations. Concentric hypertrophy, fibrosis, endothelial dysfunction, cardiomyocyte stiffness, and neurohormonal activation interact to preserve ejection fraction while impairing diastolic function, exercise capacity, and overall cardiovascular performance. Systemic comorbidities and inflammation further exacerbate remodeling, emphasizing the syndrome's complexity. A comprehensive understanding of these mechanisms is essential for the development of targeted interventions, optimized clinical management, and improved patient outcomes. Future therapeutic strategies must address both myocardial and systemic contributors to remodeling to alter the natural history of HFpEF and provide meaningful improvements in survival, functional capacity, and quality of life. Ultimately, elucidating the intricate network of remodeling pathways in HFpEF provides a foundation for advancing precision cardiovascular medicine and transforming the care of patients with this challenging syndrome.

Disclosure Statement

No potential conflict of interest reported by the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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