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Microcirculatory Dynamics in Different Phenotypes of Chronic Heart Failure

Nizamova N. G.*, Agababyan I. R.

Samarkand State Medical University, Samarkand, Uzbekistan

Abstract Heart failure (HF) represents a multifaceted syndrome wherein dysfunction of the microcirculation plays a significant role in the progression of the disease and the occurrence of adverse outcomes. This review delves into the pathophysiological mechanisms that underlie microvascular impairment across various HF phenotypes, encompassing heart failure with reduced ejection fraction (HFrEF), preserved ejection fraction (HFpEF), and mildly reduced ejection fraction (HFmrEF). Endothelial dysfunction, capillary rarefaction, and impaired vasoreactivity are fundamental to the microvascular abnormalities associated with HF. While guideline-directed medical therapy (GDMT) aspires to enhance cardiac function, its direct impact on microcirculation continues to be the subject of ongoing research. Recent advancements in biomarker research have unveiled novel indicators of microvascular health, including endothelin-1, asymmetric dimethylarginine, circulating microRNAs, and markers of endothelial glycocalyx degradation, thereby presenting new opportunities for risk stratification and early intervention. Personalized therapy, which incorporates genetic profiling, pharmacogenomics, and assessment of endothelial function, has emerged as a promising strategy for optimizing the efficacy of treatment. Furthermore, innovative microvascular-targeted interventions, such as endothelial-protective agents, therapies that promote angiogenesis, and regenerative cell-based treatments, possess the potential to restore the integrity of the microvasculature. Notwithstanding these advancements, challenges remain in the standardization of techniques for assessing microcirculation and in the implementation of microvascular therapies within the routine management of HF. Future research endeavors should prioritize the integration of microcirculatory endpoints into clinical practice to enhance therapeutic strategies and improve patient outcomes.

Keywords Heart failure, Microcirculation, Endothelial dysfunction, Biomarkers, Personalized therapy

1. Introduction

Heart failure (HF) remains a significant global health challenge, affecting millions of individuals and contributing to high morbidity and mortality rates. Despite advancements in pharmacological and non-pharmacological management strategies, HF continues to impose substantial economic and healthcare burdens. One of the key pathophysiological mechanisms underlying HF progression is microcirculatory dysfunction, which significantly impacts myocardial perfusion, tissue oxygenation, and overall cardiac function. Understanding the dynamic changes within the microcirculatory bed in different HF phenotypes is crucial for optimizing treatment strategies and improving patient outcomes [1,2].

Heart Failure (HF) is a heterogeneous clinical syndrome characterized by impaired cardiac function, leading to inadequate perfusion of peripheral tissues. Based on left ventricular ejection fraction (LVEF), HF is classified into three primary phenotypes, each with distinct pathophysiological mechanisms, clinical presentations, and therapeutic implications [3].

Heart Failure with Reduced Ejection Fraction (HFrEF, LVEF < 40%)

HFrEF is primarily characterized by significant systolic dysfunction, where the left ventricle fails to eject sufficient blood during systole. This phenotype is associated with progressive ventricular remodeling, including chamber dilatation, increased wall stress, and fibrosis [4]. Neurohormonal activation, involving the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS), plays a crucial role in disease progression. Elevated levels of natriuretic peptides (e.g., BNP, NT-proBNP) reflect the increased myocardial wall stress. The primary treatment strategy for HFrEF focuses on neurohormonal modulation through RAAS inhibitors, beta-blockers, mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter-2 inhibitors (SGLT2i), all of which have demonstrated mortality benefits [5].

* Corresponding author:
res.ssmu@gmail.com (Nizamova N. G.)
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Heart Failure with Preserved Ejection Fraction (HFpEF, LVEF ≥ 50%)

HFpEF represents a distinct pathophysiological entity driven by diastolic dysfunction, endothelial dysfunction, and systemic microvascular inflammation. Unlike HFrEF, ventricular systolic function remains relatively preserved, but the myocardium exhibits increased stiffness, impairing left ventricular relaxation and filling [6,7]. Chronic systemic inflammation, often associated with comorbidities such as hypertension, obesity, diabetes mellitus, and chronic kidney disease, leads to microvascular rarefaction and increased extracellular matrix deposition. Elevated left atrial pressures and pulmonary hypertension further exacerbate symptoms. Given the absence of well-established disease-modifying therapies, current management strategies focus on volume control, blood pressure optimization, and addressing underlying comorbidities. Recent evidence suggests that SGLT2 inhibitors and aldosterone antagonists may provide benefit in select HFpEF patients [8].

Heart Failure with Mildly Reduced Ejection Fraction (HFmrEF, LVEF 40–49%)

HFmrEF represents an intermediate phenotype that shares overlapping characteristics with both HFrEF and HFpEF. Although its pathophysiology remains an area of active investigation, evidence suggests that patients with HFmrEF may exhibit varying degrees of systolic and diastolic dysfunction, with neurohormonal activation patterns resembling HFrEF [9]. Recent clinical trials indicate that HFmrEF patients respond favorably to guideline-directed medical therapy (GDMT) traditionally used in HFrEF, including RAAS inhibitors, beta-blockers, MRAs, and SGLT2 inhibitors. However, unlike HFrEF, the degree of fibrosis and microvascular dysfunction in HFmrEF is more heterogeneous, necessitating further research into tailored therapeutic strategies [10].

Microcirculatory Dysfunction and Therapeutic Considerations

Each HF phenotype exhibits distinct microvascular abnormalities, influencing myocardial perfusion, oxygen supply-demand balance, and endothelial-dependent vasodilation. In HFrEF, reduced cardiac output leads to systemic hypoperfusion, triggering compensatory vasoconstriction and sympathetic overactivity, which further impairs coronary microvascular function. In HFpEF, increased vascular stiffness, endothelial dysfunction, and pro-inflammatory cytokine activation contribute to impaired myocardial relaxation and reduced capillary density. These differences underscore the need for phenotype-specific interventions to optimize outcomes [11].

Emerging pharmacological targets, including soluble guanylate cyclase (sGC) stimulators, GLP-1 receptor agonists, and anti-inflammatory agents, hold promise in addressing the underlying microvascular dysfunction in HF phenotypes. As research progresses, a more refined understanding of phenotype-specific mechanisms may lead to the development of precision medicine approaches for HF management [12].

2. Materials and Methods

Literature Review

Literature Review

A comprehensive literature review was conducted to explore the role of microcirculation in heart failure (HF), the assessment methods used to evaluate microvascular function, and the impact of standard therapy on microcirculatory dynamics. The databases searched included PubMed, Scopus, and Google Scholar, with keywords such as "heart failure," "microcirculation," "microvascular dysfunction," "endothelial dysfunction," "capillary rarefaction," "coronary flow reserve," and "heart failure phenotypes." Studies were selected based on their relevance, methodological rigor, and contribution to understanding the interplay between microcirculatory alterations and HF progression.

Inclusion and Exclusion Criteria

The inclusion criteria encompassed peer-reviewed original research articles, clinical trials, systematic reviews, and meta-analyses published in English within the last 20 years. Articles focusing on the pathophysiological mechanisms of microcirculatory dysfunction in HF, non-invasive and invasive methods for microvascular assessment, and the impact of HF therapies on endothelial recovery were prioritized. Studies that exclusively examined macrovascular function or were not directly related to microcirculation in HF were excluded. Additionally, non-peer-reviewed sources, conference abstracts without full publications, and articles in languages other than English were not considered.

Data Extraction

A structured approach was employed for data extraction. Key information related to pathophysiological mechanisms of microvascular dysfunction, differences in endothelial responses across HF phenotypes, techniques for assessing microcirculation, and therapeutic interventions targeting endothelial recovery and vascular remodeling was systematically collected. Special emphasis was placed on comparative analyses of HFrEF, HFpEF, and HFmrEF, highlighting the variations in microvascular involvement and treatment responses. Data were categorized into themes such as mechanistic insights, diagnostic methodologies, and therapeutic strategies for targeted analysis.

Analysis

The extracted data were analyzed to identify common trends, emerging therapeutic targets, and phenotype-specific microvascular alterations in HF. Studies reporting on non-invasive and invasive assessment techniques were compared to evaluate their clinical applicability and diagnostic accuracy. The impact of standard HF therapies on vascular remodeling, endothelial function, and capillary density was assessed, with a particular focus on how different HF phenotypes respond to treatment. Prognostic

implications of microcirculatory dysfunction were also examined to understand its role in disease progression and treatment outcomes.

Ethical Considerations

As this study was based on a literature review, there were no ethical concerns involving human or animal subjects. All sources were appropriately cited to acknowledge original authorship and maintain academic integrity.

Limitations

The primary limitation of this review is its reliance on existing literature, which may introduce potential biases related to publication quality and study availability. The heterogeneity in methodologies across different studies assessing microvascular function in HF poses a challenge in drawing uniform conclusions. Further prospective cohort studies and randomized controlled trials with standardized microcirculatory assessments are necessary to validate the findings and improve clinical decision-making in HF management.

3. Results

The Role of Microcirculation in Cardiac Pathophysiology

The microcirculation, consisting of arterioles, capillaries, and venules, is fundamental in maintaining myocardial oxygen delivery and systemic perfusion. In heart failure (HF), microcirculatory dysfunction plays a crucial role in disease progression by contributing to impaired myocardial remodeling, inadequate tissue oxygenation, and systemic congestion. This dysfunction is primarily driven by endothelial impairment, capillary rarefaction, increased vascular permeability, and coronary microvascular dysfunction, each of which exacerbates cardiac dysfunction and worsens clinical outcomes [13,14].

Endothelial dysfunction is one of the earliest and most significant manifestations of microcirculatory impairment in HF. The loss of endothelial nitric oxide (NO) bioavailability leads to impaired vasodilation, increased vascular resistance, and heightened oxidative stress. The accumulation of reactive oxygen species (ROS) further damages endothelial cells and promotes a pro-inflammatory state, which perpetuates vascular stiffness and reduces the ability of the microcirculation to regulate perfusion according to metabolic demands [15,16].

Capillary rarefaction, characterized by a progressive reduction in microvascular density, further exacerbates myocardial oxygen supply-demand imbalance. The loss of capillaries results in regional hypoxia, which stimulates maladaptive fibrotic remodeling, increases myocardial stiffness, and accelerates ventricular dysfunction. In HFpEF, microvascular dysfunction is particularly relevant, as systemic inflammation and endothelial dysfunction contribute to increased left ventricular stiffness, impaired relaxation, and elevated filling pressures [13,17].

Increased vascular permeability and venous congestion in HF lead to interstitial edema, which disrupts oxygen diffusion and impairs myocardial cellular metabolism. The extravasation of fluid into surrounding tissues creates a hypoxic environment that enhances fibrotic signaling pathways, leading to progressive diastolic dysfunction and worsening heart failure symptoms. In addition, coronary microvascular dysfunction can induce myocardial ischemia even in the absence of obstructive coronary artery disease. Reduced coronary flow reserve (CFR) is commonly observed in HF, particularly in HFpEF, where systemic inflammation and vascular stiffness further compromise myocardial perfusion [18].

Addressing microcirculatory dysfunction has become a key focus in HF management, with emerging therapeutic strategies targeting endothelial function, inflammation, and myocardial metabolism. Soluble guanylate cyclase (sGC) stimulators and GLP-1 receptor agonists have shown promise in improving endothelial function and enhancing vasodilation. Anti-inflammatory approaches, including SGLT2 inhibitors, IL-1 blockers, and colchicine, may attenuate systemic inflammation and protect against capillary loss. Additionally, metabolic modulators such as trimetazidine and ranolazine aim to optimize myocardial efficiency by improving oxygen utilization and reducing ischemic injury [19].

Advancements in microvascular imaging and biomarker research have provided valuable insights into the pathophysiology of HF-related microvascular dysfunction. Non-invasive techniques such as myocardial contrast echocardiography (MCE) and cardiac magnetic resonance (CMR) perfusion imaging enable more precise assessment of coronary microvascular function, while biomarkers such as endothelin-1 serve as potential indicators of endothelial health. Integrating microvascular dysfunction assessment into routine HF evaluation may facilitate personalized therapeutic approaches and improve clinical outcomes, underscoring the importance of microcirculation in cardiac pathophysiology [20,21].

Methods for Assessing Microcirculation in Heart Failure

The assessment of microcirculatory function in heart failure (HF) is essential for understanding disease progression, guiding therapeutic strategies, and evaluating response to treatment. Both non-invasive and invasive techniques have been developed to evaluate endothelial function, capillary integrity, and myocardial perfusion efficiency [17,22].

Non-invasive methods provide valuable insights into systemic microvascular function without the need for catheter-based interventions. Nailfold capillaroscopy is a widely used technique that allows for the visualization of microvascular architecture, capillary density, and blood flow patterns in the nailfold region. This method is particularly useful in detecting microvascular rarefaction and endothelial abnormalities in HF patients with systemic vascular involvement. Laser Doppler flowmetry measures skin perfusion by assessing real-time microvascular blood flow changes in response to various stimuli, providing an indirect but reliable indicator of endothelial function and

peripheral vascular reactivity. Another commonly used approach is peripheral arterial tonometry, which evaluates endothelial-dependent vasodilation by assessing pulse amplitude changes in response to reactive hyperemia. This technique provides a non-invasive means of quantifying endothelial dysfunction, a key contributor to HF pathophysiology [13,23].

Invasive techniques offer direct and precise evaluation of myocardial microvascular function. Coronary flow reserve (CFR) measurement is a well-established method that assesses the ability of coronary circulation to increase blood flow in response to increased metabolic demands. A reduced CFR is indicative of coronary microvascular dysfunction, particularly in HFpEF, where impaired myocardial perfusion occurs despite the absence of obstructive coronary artery disease. Intravascular imaging modalities such as optical coherence tomography (OCT) and intravascular ultrasound (IVUS) provide high-resolution visualization of coronary vessel morphology, allowing for the identification of microvascular obstructions, endothelial thickening, and functional impairments that contribute to HF progression [24,25].

The integration of these assessment methods into clinical practice enhances the ability to characterize microvascular dysfunction across different HF phenotypes. Non-invasive approaches serve as valuable screening tools, while invasive techniques provide detailed mechanistic insights that can inform personalized therapeutic strategies. Ongoing advancements in microvascular imaging and functional testing continue to refine the understanding of microcirculatory abnormalities in HF, highlighting the need for targeted interventions to improve patient outcomes [26,27].

The management of heart failure (HF) involves a combination of pharmacological and non-pharmacological interventions, many of which have significant effects on microcirculatory function. Given that microvascular dysfunction plays a pivotal role in HF progression, understanding the impact of these therapeutic strategies on endothelial function, capillary perfusion, and myocardial oxygen delivery is crucial for optimizing treatment outcomes [28].

Pharmacological Therapy and Microcirculatory Effects

Angiotensin-Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockers (ARBs) play a central role in HF management by reducing afterload, preventing maladaptive cardiac remodeling, and improving endothelial function. These agents enhance nitric oxide (NO) bioavailability, reduce oxidative stress, and inhibit vascular inflammation, thereby promoting vasodilation and improving microvascular perfusion. The attenuation of renin-angiotensin-aldosterone system (RAAS) overactivation also mitigates capillary rarefaction and improves tissue oxygenation [19].

Beta-Blockers contribute to hemodynamic stabilization by reducing heart rate, myocardial oxygen demand, and sympathetic overactivation, all of which are essential in protecting the microcirculation. By decreasing adrenergic-mediated vasoconstriction, beta-blockers improve coronary microvascular reserve and facilitate capillary recruitment, enhancing perfusion at the tissue level. In addition, long-term beta-blockade has been shown to reduce endothelial apoptosis, preserving microvascular integrity in HF patients [29,30].

Mineralocorticoid Receptor Antagonists (MRAs) such as spironolactone and eplerenone exert anti-fibrotic and anti-inflammatory effects, which indirectly benefit the microcirculation. These agents reduce myocardial and vascular fibrosis, leading to improved compliance of the coronary and systemic microvasculature. Their diuretic effect also alleviates venous congestion, reducing microvascular permeability and interstitial edema, which are common contributors to impaired oxygen diffusion in HF [31].

Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors have emerged as novel agents with beneficial effects on microcirculatory dynamics in HF. Initially developed for glycemic control in diabetes, SGLT2 inhibitors such as dapagliflozin and empagliflozin have demonstrated improvements in vascular endothelial function, capillary perfusion, and mitochondrial efficiency. These agents modulate inflammatory signaling, reduce oxidative stress, and enhance NO availability, leading to improved microvascular autoregulation and better myocardial oxygen supply [32,33].

Ivabradine, Nitrates, and Other Vasodilators also play an essential role in modifying microvascular function. Ivabradine, by selectively reducing heart rate without affecting contractility, improves coronary diastolic perfusion, thereby enhancing microvascular oxygenation. Nitrates and other vasodilators act primarily through NO-mediated pathways, improving endothelial function, increasing capillary recruitment, and reducing vascular stiffness. However, their efficacy in HFpEF remains less well established, highlighting the need for further research into phenotype-specific microvascular responses [33].

Non-Pharmacological Interventions and Microcirculatory Health

Beyond pharmacological therapy, lifestyle modifications and non-pharmacological interventions play a critical role in preserving and restoring microvascular function in HF. Regular physical exercise has been shown to improve endothelial-dependent vasodilation, enhance capillary density, and reduce systemic inflammation. Both aerobic and resistance training contribute to improved microvascular perfusion by increasing shear stress-mediated NO production, stimulating angiogenesis, and improving mitochondrial efficiency in cardiac and skeletal muscle [34].

Dietary modifications also influence endothelial health and microcirculatory function. Diets rich in omega-3 fatty acids, polyphenols, and antioxidants promote endothelial repair mechanisms, enhance NO bioavailability, and reduce oxidative stress. Sodium restriction and adherence to a Mediterranean or DASH (Dietary Approaches to Stop Hypertension) diet have demonstrated beneficial effects in reducing vascular inflammation and improving endothelial responsiveness in HF patients [35,36].

Integrating both pharmacological and non-pharmacological strategies into HF management is crucial for optimizing microcirculatory function and preventing further deterioration of myocardial perfusion. As research advances, targeting phenotype-specific microvascular dysfunction may enable more personalized treatment approaches, ultimately improving clinical outcomes in HF patients.

Comparative Analysis of Microcirculatory Changes Across HF Phenotypes

Microcirculatory dysfunction plays a crucial role in the pathogenesis and progression of heart failure (HF), with distinct alterations observed across different phenotypes. While heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF), and heart failure with mildly reduced ejection fraction (HFmrEF) share common underlying mechanisms, their microvascular responses to therapy, endothelial recovery patterns, and long-term prognostic implications vary significantly [37,38].

Response to Standard Therapy

In HFrEF, microcirculatory dysfunction is primarily driven by impaired myocardial perfusion, neurohormonal activation, and capillary rarefaction due to ongoing ventricular remodeling. Standard therapy, including RAAS inhibitors, beta-blockers, mineralocorticoid receptor antagonists (MRAs), and SGLT2 inhibitors, has been shown to ameliorate endothelial dysfunction, reduce oxidative stress, and improve coronary flow reserve (CFR). These agents contribute to vascular stabilization and attenuate capillary dropout, ultimately improving microcirculatory dynamics in patients with HFrEF [39,40].

In contrast, HFpEF is characterized by systemic endothelial dysfunction, increased vascular stiffness, and microvascular inflammation. Traditional HFrEF therapies have demonstrated limited efficacy in this phenotype, as microvascular dysfunction in HFpEF is more inflammatory and metabolic in origin rather than neurohormonally driven. SGLT2 inhibitors, which have shown benefit in HFpEF, are believed to improve endothelial function, reduce microvascular congestion, and enhance myocardial energy efficiency. Other potential therapeutic approaches targeting inflammation, oxidative stress, and NO signaling pathways are currently under investigation to improve microvascular health in HFpEF patients [41].

HFmrEF represents an intermediate phenotype with overlapping characteristics of both HFrEF and HFpEF. Emerging evidence suggests that HFmrEF patients exhibit variable responses to standard HF therapies, with some individuals showing improvements in microvascular perfusion and endothelial function following neurohormonal blockade, while others display persistent vascular stiffness and inflammatory activation similar to HFpEF. Given this heterogeneity, optimizing treatment in HFmrEF requires further investigation to determine the most effective microvascular-targeted interventions.

Differences in Endothelial Recovery and Remodeling

Endothelial recovery and vascular remodeling differ markedly between HF phenotypes. In HFrEF, progressive left ventricular dilation and wall stress contribute to coronary microvascular dysfunction, but early therapeutic intervention with beta-blockers, RAAS inhibitors, and SGLT2 inhibitors can facilitate vascular repair, restore endothelial integrity, and enhance capillary perfusion. The dynamic nature of ventricular reverse remodeling in response to therapy often correlates with improvements in microcirculatory function [4].

In HFpEF, endothelial dysfunction is primarily driven by chronic inflammation, metabolic dysregulation, and microvascular stiffening, leading to poor endothelial recovery even in response to therapy. Vascular remodeling in HFpEF is characterized by increased extracellular matrix deposition, impaired nitric oxide signaling, and reduced capillary recruitment, all of which contribute to persistent diastolic dysfunction. Unlike HFrEF, where vascular remodeling is partially reversible, the structural changes in HFpEF microcirculation tend to be more fibrotic and resistant to intervention, necessitating novel anti-inflammatory and endothelial-stabilizing therapeutic approaches [10].

HFmrEF presents a more heterogeneous pattern of vascular remodeling, with some patients exhibiting adaptive endothelial responses similar to HFrEF, while others experience persistent microvascular dysfunction akin to HFpEF. This variability highlights the need for personalized therapeutic approaches based on specific microcirculatory and endothelial profiles in HFmrEF patients [10].

Prognostic Implications of Microcirculatory Dysfunction

The degree of microvascular dysfunction is a critical determinant of clinical outcomes across all HF phenotypes. In HFrEF, persistent capillary rarefaction and impaired myocardial perfusion are associated with an increased risk of arrhythmias, worsening heart failure, and sudden cardiac death. However, patients who exhibit microvascular recovery following standard therapy tend to have better long-term survival and reduced hospitalization rates [9,11].

In HFpEF, microvascular dysfunction is highly predictive of exercise intolerance, pulmonary hypertension, and adverse cardiovascular events. The lack of effective microvascular-targeted therapies in HFpEF further exacerbates the prognosis, as persistent endothelial dysfunction contributes to progressive ventricular stiffening and hemodynamic congestion. Given that microvascular dysfunction is strongly linked to worsening diastolic dysfunction, it remains a crucial area for future therapeutic advancements [42].

HFmrEF patients exhibit intermediate prognostic outcomes, with those displaying HFrEF-like microvascular impairment having a higher likelihood of disease progression, while those with HFpEF-like endothelial dysfunction often develop worsening vascular inflammation and metabolic disturbances. Given the evolving classification of HFmrEF, further studies are needed to establish prognostic biomarkers that accurately stratify patients based on microvascular health [43].

Microcirculatory dysfunction is a shared but phenotype-specific feature of HF, influencing disease progression, therapeutic response, and long-term prognosis. While traditional HFrEF therapies target neurohormonal and hemodynamic pathways to restore microvascular function, HFpEF remains a challenge due to its distinct inflammatory and endothelial-driven pathophysiology. HFmrEF, as an evolving entity, presents a heterogeneous microvascular profile, necessitating personalized therapeutic strategies. Future research should focus on developing precision medicine approaches that integrate microvascular imaging, endothelial biomarkers, and targeted pharmacological interventions to improve patient outcomes across all HF phenotypes [37,41].

Future Perspectives and Research Directions

Advancements in biomarker research have opened new avenues for assessing microcirculatory function in heart failure (HF). Traditional markers such as NT-proBNP and troponins provide insights into cardiac stress and injury but do not directly evaluate microvascular health. Emerging biomarkers of endothelial function and microvascular integrity could provide a more targeted approach for identifying microcirculatory dysfunction and guiding therapeutic decisions. Among them, endothelin-1 (ET-1) has been recognized as a potent vasoconstrictor involved in endothelial dysfunction, with elevated levels correlating with impaired microvascular perfusion and increased mortality in HF patients. Similarly, asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase, plays a crucial role in nitric oxide dysregulation, endothelial dysfunction, and increased vascular stiffness, all of which contribute to HF progression [43]. Circulating microRNAs, particularly miR-126 and miR-223, have emerged as key regulators of endothelial repair, angiogenesis, and inflammatory modulation, with altered expression profiles serving as potential indicators of microvascular damage. Furthermore, the degradation of the endothelial glycocalyx, reflected by elevated levels of syndecan-1 and heparan sulfate, represents another important aspect of microvascular impairment, particularly in HFpEF and HFmrEF. In addition to these circulating biomarkers, non-invasive imaging techniques such as contrast-enhanced ultrasound, optical coherence tomography (OCT), and near-infrared spectroscopy (NIRS) are gaining attention as valuable tools for real-time microcirculatory assessment. The integration of these biomarkers and imaging techniques into clinical practice holds promise for early detection, phenotypic differentiation, and risk stratification of HF patients. Future research should focus on developing multi-biomarker panels that combine biochemical, imaging, and functional parameters to enhance diagnostic accuracy and therapy monitoring [44,45].

Given the heterogeneity of HF phenotypes and their distinct microcirculatory alterations, personalized therapy holds significant potential in optimizing treatment responses. The concept of precision medicine in HF is gaining momentum, shifting from a uniform approach to a tailored strategy based on individual endothelial and inflammatory profiles. Genetic and epigenetic profiling can help identify patient subgroups with specific microvascular impairments, while pharmacogenomics can refine drug therapy by accounting for individual variations in drug metabolism and receptor sensitivity. Understanding polymorphisms in beta-adrenergic receptors or the renin-angiotensin system could enhance the effectiveness of beta-blockers, RAAS inhibitors, and SGLT2 inhibitors. Moreover, targeted neurohormonal modulation, guided by endothelial function markers, could allow for more precise adjustments in medication regimens, minimizing side effects while maximizing therapeutic benefits. Beyond pharmacotherapy, lifestyle and metabolic interventions play a crucial role in improving microvascular function. Structured exercise programs tailored to microvascular dysfunction have been shown to enhance capillary recruitment and endothelium-dependent vasodilation, particularly in patients with HFpEF [10,15,23]. Dietary interventions, such as nitrate-rich diets, have demonstrated the potential to improve nitric oxide bioavailability and endothelial health. Furthermore, metabolic control through GLP-1 receptor agonists and SGLT2 inhibitors offers promising avenues for reducing endothelial inflammation and oxidative stress, thereby exerting protective effects on the microcirculation. To validate these approaches, future clinical trials should incorporate microcirculatory endpoints alongside conventional cardiac function parameters, ensuring that therapeutic strategies adequately address both macrovascular and microvascular dysfunction in HF. The integration of multi-omics approaches, including genomics, proteomics, and metabolomics, may further refine patient stratification and enhance our understanding of microvascular heterogeneity in HF [1].

While current HF therapies exert indirect effects on microcirculation, novel interventions specifically targeting endothelial and capillary function are under active investigation. Several promising strategies aim to directly modulate endothelial integrity, vascular tone, and inflammatory pathways to restore microvascular function [13,21,27]. Endothelial-protective agents such as soluble guanylate cyclase (sGC) stimulators, including vericiguat, have shown potential in enhancing nitric oxide-cGMP signaling, leading to improved endothelial function and microvascular dilation. Nitric oxide donors, such as molsidomine and sodium nitroprusside, may also enhance endothelium-dependent vasodilation in patients with endothelial dysfunction and microvascular ischemia. Angiogenesis-promoting therapies, including vascular endothelial growth factor (VEGF) agonists, are being explored to counteract microvascular rarefaction, a hallmark of HFpEF and HFmrEF, while hypoxia-inducible factor (HIF) stabilizers are emerging as potential regulators of adaptive responses to myocardial hypoxia. In parallel, anti-inflammatory and antifibrotic agents such as IL-1 inhibitors, including anakinra and canakinumab, are being investigated for their ability to reduce systemic and endothelial inflammation, thereby improving microvascular endothelial integrity. The inhibition of galectin-3, a key mediator of fibrotic remodeling in the

microcirculation, is another avenue with potential benefits, particularly in HFpEF patients with extensive capillary rarefaction. Beyond pharmacological interventions, regenerative therapies such as mesenchymal stem cell transplantation and endothelial progenitor cell therapy are being explored for their ability to enhance capillary density and restore endothelial function in patients with refractory HF [4,6].

Despite the promising results seen in preclinical models and early-phase clinical trials, several challenges must be addressed before these targeted microvascular interventions can be widely implemented in clinical practice. The heterogeneity of microvascular pathology across different HF phenotypes necessitates a more personalized therapeutic approach, as not all patients exhibit the same degree of endothelial dysfunction or capillary rarefaction. Additionally, the lack of standardized assessment tools for evaluating microcirculatory function poses a significant barrier to clinical translation. While several non-invasive techniques exist, their widespread adoption is limited by cost, availability, and operator dependence. Another critical challenge is the gap between experimental findings and real-world applicability [46]. Many promising microvascular therapies lack large-scale, multicenter trial data, making it difficult to assess their long-term clinical efficacy and safety. Furthermore, the potential for unintended systemic effects, such as hypotension, excessive vasodilation, or pro-inflammatory activation, underscores the need for cautious implementation. Future research should prioritize large, randomized controlled trials that incorporate microvascular-specific endpoints and assess long-term outcomes. Additionally, integrating biomarker-driven decision-making into routine HF management could enable earlier intervention and more precise risk stratification, ultimately improving patient outcomes. As our understanding of microcirculatory dysfunction in HF evolves, a comprehensive, multi-disciplinary approach that combines innovative diagnostics, precision therapeutics, and targeted interventions will be essential for optimizing microvascular health and reducing the burden of HF [47,48].

4. Conclusions

Microcirculatory dysfunction plays a crucial role in the pathophysiology of HF, contributing to impaired perfusion, endothelial dysfunction, and progressive myocardial damage. Different HF phenotypes exhibit distinct microvascular alterations, necessitating phenotype-specific therapeutic approaches. While guideline-directed medical therapy (GDMT) improves cardiac function, its direct impact on microcirculation remains an evolving field of research. Emerging biomarkers, personalized treatment strategies, and novel vascular-targeted interventions hold promise for optimizing HF management.

Integrating microcirculatory assessment into routine HF care can provide valuable insights into disease progression and treatment response. Biomarkers of endothelial function, advanced imaging techniques, and functional assessments of capillary perfusion may serve as crucial tools for risk stratification and therapy optimization. Understanding microvascular dynamics could enhance therapeutic decision -making, particularly in HFpEF and HFmrEF, where conventional treatment strategies remain less defined.

Given the pathophysiological heterogeneity of HF, a one-size-fits-all approach may not be sufficient. Future HF treatment paradigms should incorporate microvascular considerations, tailoring interventions based on endothelial function, inflammatory status, and capillary integrity. Addressing microcirculatory dysfunction may not only improve cardiac function but also enhance systemic perfusion and overall patient outcomes.

In conclusion, a deeper understanding of microvascular alterations in HF and their modulation by basic therapy can lead to more precise, effective, and patient-centered therapeutic strategies. Ongoing research efforts should focus on refining microcirculatory diagnostics, advancing targeted interventions, and integrating personalized medicine into HF management.

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