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Coronary microvascular dysfunction and its role in heart failure with preserved ejection fraction for future prevention and treatment

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HIGHLIGHTS

- Coronary microvascular dysfunction may play a role in development of HFpEF.
- Common cardiometabolic risk factors contributing ot HfpEF create a pro-inflammatory environment that leads to endothelial dysfunction and improper regulation of vasoactive substances, impaired coronary blood flow.
- Increased research is needed to have targeted therapies to best manage coronary microvascular dysfunction.
- The literature review explores how race, ethnicity, sex, gender, and social determinants of health impact the disparate health outcomes for those at risk for CMD and HFpEF.

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ABSTRACT

Ischemic heart disease has long been established as the leading cause of heart failure, typically as a result of hemodynamically significant and obstructive coronary anatomy. Since, the role of dysfunctional coronary microvascular pathophysiologic mechanisms have also been associated with the development of congestive heart failure (CHF), most notably heart failure with preserved ejection fraction (HFpEF) although with limited clinical evidence. Conventional cardiometabolic and behavioral risk factors common to HFpEF such as diabetes mellitus (DM), obesity, hypertension, dyslipidemia, smoking, and chronic kidney disease foster a pro-inflammatory environment conducive to endothelial dysfunction and improper regulation of vasoactive substances. The impaired relaxation and increased vasoconstriction of damaged endothelium gives rise to impaired coronary blood flow and episodes of transient ischemia. Such coronary microvascular dysfunction (CMD) has its own implication on cardiovascular pathophysiologic mechanisms beyond symptomatic coronary and myocardial ischemia, and thus its own potential prevention goals and treatment targets for patients with HFpEF, where previous management had been limited. As such, we conducted a literature review to address the current landscape of data which links CMD to HFpEF. Furthermore, we considered the implications of biopsychosocial

Abbreviations: IHD, ischemic heart disease; CHF, congestive heart failure; HFpEF, heart failure with preserved ejection fraction; DM, diabetes mellitus; CKD, chronic kidney disease; CBF, coronary blood flow; CMD, coronary microvascular dysfunction; CAD, coronary artery disease; HFrEF, heart failure with reduced ejection fraction; INOCA, ischemia and no obstructive coronary arteries; MACE, major adverse cardiovascular events; NO, nitric oxide; ROS, reactive oxygen species; Lp(a), lipoprotein a; CVD, cardiovascular disease; RA, rheumatoid arthritis; BEW, backwards expansion wave; PET, positron emission tomography; CMR, cardiac magnetic resonance; CT, computed Tomography; CFR, coronary flow reserve; FFR, fractional flow reserve; iCFR, invasive coronary flow reserve; ACEI, angiotensin-converting enzyme inhibitors.

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elements such as race, ethnicity, sex, gender, and the social determinants of health as they relate to the disparate health outcomes of those most at risk for CMD and HFpEF.

1. Introduction

Heart failure is a global pandemic affecting over 64 million people worldwide with expectation to surge in the coming decades due to the aging global population [1]. The universal definition of congestive heart failure (CHF) was adopted in 2021 as, "a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion" [2]. Generally, CHF is divided into three subgroups based on ejection fraction percentage: reduced, mildly reduced, and preserved.

Coronary artery disease (CAD) has been well established as the leading cause of heart disease in the United States (US) and has been considered synonymous with the term, ischemic heart disease (IHD). Nearly one in every five US adults older than 20 years old has CAD [3]. CAD is defined as atherosclerosis within the arterial walls and can be further classified into obstructive or nonobstructive disease. Obstructive CAD occurs when atherosclerotic changes result in 50–70 % luminal obstruction causing hemodynamically significant health implications often evidenced by myocardial ischemia [4]. Ischemic heart disease has long been established as the leading cause of CHF, typically as a result of such hemodynamically significant and often obstructive coronary disease.

With heart failure often an end-stage consequence of IHD, heart failure with reduced ejection fraction (HFrEF) seems to be the primary deficit exhibited. HFrEF, defined as ejection fraction $<$40 %, is often caused by CAD[1], where regional myocardial death follows chronic ischemia and myocardial remodeling or acute myocardial infarction of localized vessels and subsequent paralysis of downstream myocardial territories that impacts the pump's global efficacy.

Heart failure with preserved ejection fraction (HFpEF) includes an ejection fraction of $\geq$50 %. The pathophysiologic mechanisms resulting in HFpEF have not fully been elucidated and are likely multifactorial; however, in recent years, it has been hypothesized that conventional cardiometabolic comorbidities such as diabetes mellitus (DM), hypertension, hyperlipidemia, obesity, and chronic kidney disease (CKD) result in a persistent pro-inflammatory state with eventual development of hemodynamically significant coronary microvascular dysfunction (CMD) [5]. Since there is an increasing understanding of the progressive mechanism of IHD through inhibition of normal vasodilation, a changing paradigm has ensued where we are more aware that CMD may be a significant contributor to the development of HFpEFf [6].

As highlighted in the study by Cenko et al [7]., emerging evidence suggests that CMD occurs approximately half as frequently in association with and as a consequence of unstable angina and other acute coronary syndromes (ACS). This relationship underscores the potential for shared pathophysiological mechanisms between ACS and the development of HFpEF, particularly in patients presenting with unstable angina or non-ST-elevation myocardial infarct (NSTEMI). In these situations disruptions in coronary microcirculation, which may initially present as ischemia or anginal symptoms, can contribute to such myocardial remodeling and diastolic dysfunction over time, increasing the risk for HFpEF. This connection highlights the importance of early recognition and intervention in CMD to mitigate the progression towards heart failure.

One additional example of CMD is ischemia with nonobstructive coronary arteries (INOCA). A diagnosis of INOCA is considered when anginal symptoms and ischemia are present without obstructive CAD, defined as luminal narrowing of $<$50 % [8]. Understanding these overlapping mechanisms may improve patient stratification and facilitate the development of targeted therapies to address both ischemic and heart failure phenotypes [4]. While CMD and HFpEF affect both sexes, there is a disproportionate impact on women underscoring the importance of gender-specific research for better diagnosis, treatment strategies and to improve outcomes in women. This is best demonstrated in the fact that the key findings of a pivotal study focusing on IHD, the Women's Ischemia Syndrome Evaluation (WISE) study, was that women with signs and symptoms of INOCA often have CMD and are at an increased risk for major adverse cardiovascular events (MACE), the most prevalent of which is heart failure hospitalizations confirmed to be predominately HFpEF [9]. However, a diagnosis of CMD can often be missed when such patients are found to have evidence of other structural and functional forms of heart disease such as cardiomyopathy and heart failure due to the limited awareness of the intersection of both conditions.

2. Pathophysiology of coronary microvascular dysfunction

2.1. Coronary anatomy and physiology

The coronary microvascular circulation contributes largely to coronary resistance (Fig. 1). However, gross visualization of the coronary system, whether invasive or noninvasive, is limited to the epicardial arteries greater than 500 μm in diameter [10]. Historically, coronary microcirculation has largely been underemphasized as a dynamic participant in global myocardial function despite pre-arterioles and arterioles comprising 25 % and 50 % of coronary artery resistance respectively [5].

The main role of this system involves adapting coronary blood flow (CBF) and oxygen delivery to accommodate changes in metabolic demand and avoid myocardial ischemia. In healthy individuals, the coronary microcirculation will dilate in response to increased metabolic demand, which increases the overall CBF [5].

Throughout the vasculature, endothelium produces vasodilating substances, one of which is nitric oxide (NO). During periods of increased metabolic demand, the endothelial cells release NO to dilate the coronary arteries and increase CBF. However, when cardiometabolic risk factors foster a pro-inflammatory state, reactive oxygen species (ROS) are generated, impairing endothelial cells and NO bioavailability. This decrease in NO leads to an attenuated CBF response leading to transient myocardial ischemia. Furthermore, impaired endothelial cells induce paradoxical microvascular vasoconstriction. This shift of dominance from vasodilatory to vasoconstricting substances, also compromises CBF [11].

CMD is defined as the inability to increase CBF through the microvasculature and may also be accompanied by a reduction in CBF due to coronary microvascular spasm [5]. Structural remodeling of the microcirculation including decreased capillary density, a trait known as microvascular rarefaction, and hypertrophied luminal narrowing have also been demonstrated as drivers in the pathophysiologic process of CMD [10].

3. Risk factors that contribute to coronary microvascular dysfunction

3.1. Cardiometabolic risk factors

As previously mentioned, cardiometabolic risk factors foster a pro-inflammatory state, which have a strong correlation with CMD and eventual development of HFpEF (Fig. 2). These risk factors overlap with those which contribute to obstructive CAD including DM, obesity, hypertension, dyslipidemia, and CKD [10]. Evidence suggests individuals

may exhibit CMD in isolation of CAD; however, oftentimes CMD is present within the spectrum of atherosclerotic disease and clinically significant CAD [11]. Mitigating these modifiable risk factors are essential in circumventing CMD, similarly to CAD.

Diabetes mellitus causes well known metabolic pathologies such as hyperglycemia, chronic inflammation, oxidative stress, and diabetic cardiomyopathy. Similar to its effects in the retina and kidneys, DM can cause microvascular dysfunction in the heart and coronary vasculature [12]. Hyperglycemia can specifically impair the endothelial vasodilator substances and increase production of ROS leading to impaired CBF during states of increased myocardial demand. Advanced glycation endproducts, which are commonly seen in DM, have been illustrated to play an important role in microvascular damage through their deposition in vessels. Advanced glycation endproducts, along with insulin resistance, cause a cascade of pro-inflammatory substances and free fatty acids which further damage cardiac myocytes along with the coronary microvascular endothelium [11].

Obesity and cardiometabolic syndrome have been found to function in the destabilizing of normal endothelial functioning, resulting in reduced NO bioavailability and increased vasoconstricting substances. Other pathologies caused by metabolic dysfunctions include increased activity of the renin-angiotensin-aldosterone pathway and increased alpha-adrenergic receptors. Furthermore, increased adipocytes have been shown to curate a pro-inflammatory environment of oxidative stress and endothelial dysfunction [11]. All of these dysregulated pathways promote a lower CBF through a reduction in coronary microcirculation dilation and an increase of vasoconstriction.

Through established cytokine cascades, hypertension can cause structural remodeling in the coronary microcirculation where both small and large arteries can have hypertrophic inward remodeling and capillary rarefaction. Inward remodeling produces a narrowing of the microvasculature with an increase in media to lumen ratio [13]. These transformations can be most commonly seen in left ventricular hypertrophy in which the wall is thickened due to remodeled arterioles. Hypertension can also cause capillary rarefaction, although the mechanism is not perfectly understood [14]. The changes in the size and density of the vessels due to hypertension increases the functional deficits in CMD.

Dyslipidemia is a well-established risk factor of CAD; however, emerging evidence supports its role in the development of CMD. Reduced CBF is seen in patients with dyslipidemia, even prior to evidence of coronary stenosis. Both total cholesterol and low-density lipoprotein are inversely correlated to microvascular resistance, with both generating ROS and a subsequent inflammatory environment which is particularly harmful as oxidized low-density lipoprotein plays a detrimental role in atherosclerosis and inhibits the endothelial production of NO within the coronary microvasculature [11]. A lesser studied potential culprit within the dyslipidemia spectrum is lipoprotein(a) or Lp(a), a circulating apolipoprotein-B containing particle that is an important genetic risk factor for cardiovascular disease (CVD) [15]. Elevated levels of Lp(a) have been demonstrated to elicit arterial inflammation, atherogenesis and calcification. There is a paucity of data to exclude the possibility that Lp(a) directly influences the microvascular endothelium, making it an exciting consideration for further investigation [16].

3.2. *Additional risk factors that influence CMD*

Other risk factors including chromosomal gender/biological sex, age, race and ethnicity have been identified as relevant risk factors in the incidence of CMD. As previously mentioned, CMD has been found to be more prevalent in women than men. In a study out of Europe that included 1379 patients with angina and non-obstructed coronary arteries, vasomotor dysfunction such as CMD, occurred more often in women as compared to men [17]. The study highlighted that women experienced vasomotor dysfunction more frequently and at lower doses of acetylcholine, which suggests a heightened sensitivity in their coronary arteries. This dysfunction encompassed various mechanisms, including focal and diffuse spasm, as well as microvascular dysfunction. These findings underscore the importance of considering sex-related differences in the diagnosis and treatment of patients with INOCA. The highest prevalence of CMD exists within the postmenopausal population. Successful animal model studies support the postulation that estrogen may exhibit cardioprotective characteristics towards the development of CMD due to interplay with NO production [18]. As a

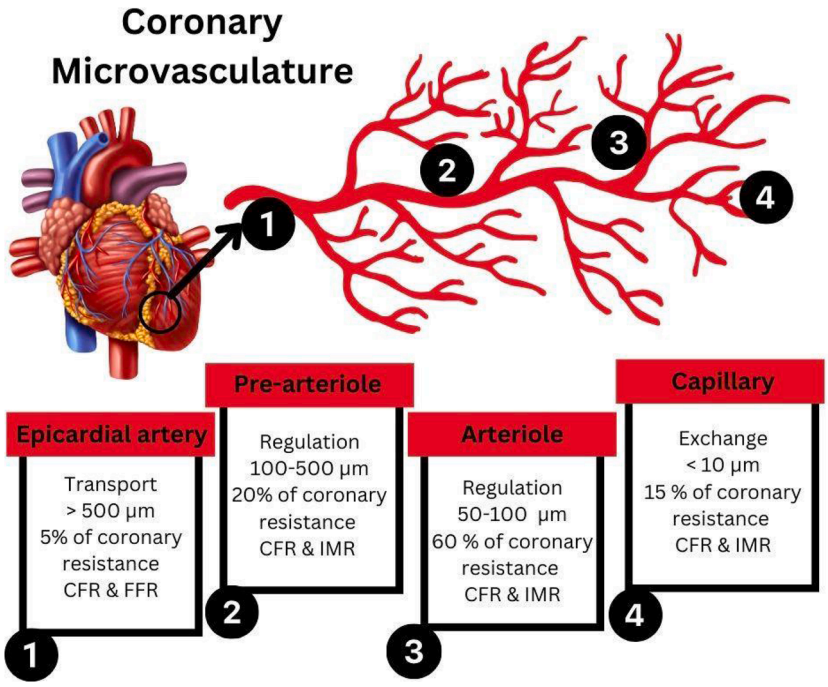

Fig. 1. The coronary vasculature consists of epicardial arteries, pre-arterioles, arterioles, and capillaries. CFR = coronary flow reserve, FFR = fractional flow reserve, IMR = index of microcirculatory resistance.

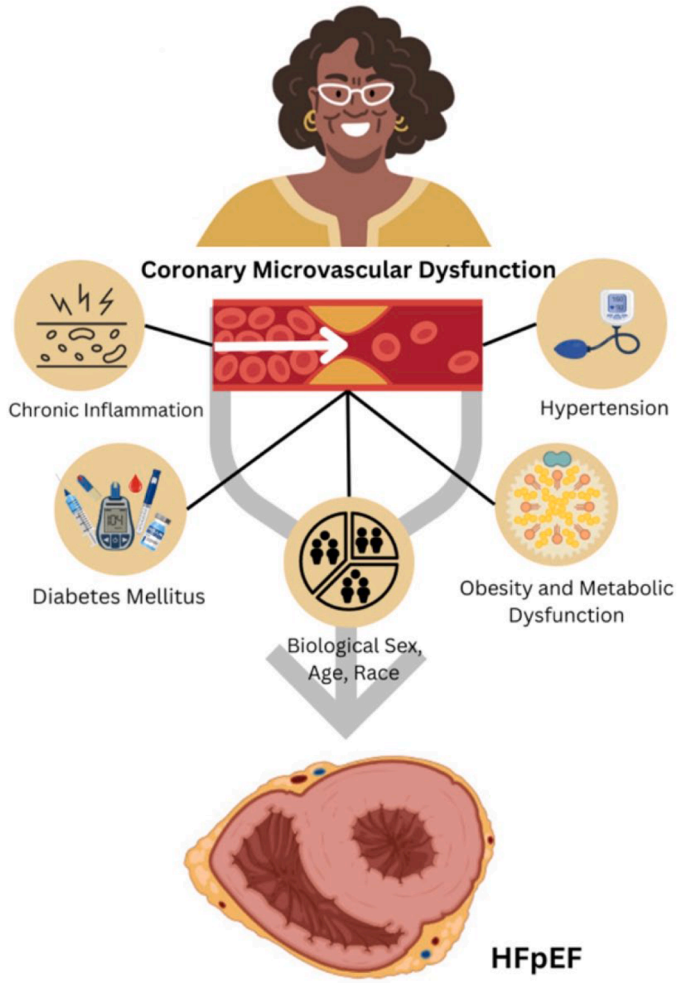

Fig. 2. Several cardiometabolic risk factors have been linked to development of CMD and development of HFpEF. HFpEF = Heart Failure with Preserved Ejection Fraction.

result of this disparity, CMD, and furthermore, HFpEF may be under-recognized and misdiagnosed in women, perpetuating the historical sex and gender bias within the field of cardiology.

Rheumatologic diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus demonstrate a higher preponderance for CHF due to mechanisms such as atherosclerosis, left ventricular diastolic dysfunction, inflammatory cytokines, nonsteroidal anti-inflammatory drug usage, and valvular heart disease [19,20]. Cytokine modulation in autoimmune diseases is postulated to be the culpable mechanism of CMD; however, this has yet to be scientifically indicted. In a systematic review of 25 studies and nearly 6000 patients with RA and HFpEF, Aslam et al. demonstrated a prevalence of diastolic dysfunction present in patients with RA [21]. It is widely accepted that diastolic dysfunction is a prevalent feature of HFpEF [22], thus there is much to be demonstrated regarding the role these autoimmune processes play in the development of HFpEF.

4. Pathophysiology of microvascular dysfunction in heart failure with preserved ejection fraction

The incidence of HFpEF has been increasing worldwide in recent years. The rise in prevalence is likely as a result of an increased awareness, but may also be related to the increase in the conventional cardiometabolic risk factors that contribute to it. Unfortunately, the true pathophysiology behind HFpEF is not fully understood. HFpEF is defined as a preserved systolic cardiac function with left ventricular diastolic dysfunction, but left atrial dysfunction, right ventricular dysfunction, and diffuse myocardial thickening can also be seen [23].

Fundamental gaps exist between our understanding of the pathophysiologic relationship between CMD and HFpEF. HFpEF has been postulated as being more of a systemic syndrome, than an isolated coronary pathology [11]. This is best highlighted by the proposition that HFpEF is caused by the pro-inflammatory state of CMD characterized by ventricular hypertrophy, myocardial fibrosis, left atrial dilation, left ventricular stiffness and diastolic dysfunction· These features are created by a more generalized, systemic CMD, consisting of both coronary and peripheral microvascular dysfunction within vascular beds other than the heart [24].

Two of the phases of coronary flow are the early forwards compression wave, which is caused by left ventricular compression ejecting the blood to the body, and the backwards expansion wave (BEW), which is caused by the relaxation of the left ventricle during diastole [25]. In a healthy individual, the majority of coronary blood flow occurs during the BEW, diastolic relaxation or coronary microcirculatory decompression. In CMD, due to the endothelial dysfunction causing decrease in vasodilation, BEW is shown to be slowed. It is proposed that due to CMD, there is decreased lusitropy, or the degree of left ventricle relaxation causing diastolic dysfunction, a halt in BEW and decrease in myocardial perfusion [6]. Although the evidence is accumulating, more studies are needed to confirm the progression of CMD as a causative reason for HFpEF.

4.1. Stable ischemic disease, CMD and HFpEF

Though CMD is not necessarily mutually exclusive of obstructive CAD and/or epicardial IHD, further evidence of the relationship between CMD and HFpEF is suggested by data which relates stable IHD as it pertains to angina to HFpEF. Relatively little is known about the significance of stable angina within HFpEF populations; however it is accepted that angina often has a higher prevalence in HFrEF populations rather than HFpEF. Nevertheless, in a Duke study of 3517 patients with HFpEF and previous angiography, 40 % were found to have complaints of angina after adjusting for guideline-directed medical therapy and previous revascularization [26]. Their study revealed those with recent angina had an increased risk of MACE. These findings lend evidence to support the need for a more inclusive management paradigm that uncouples the singular association between epicardial CAD and revascularization, and better aligns diagnostic approaches that tailor treatment to the underlying mechanisms and precipitants of angina and ischemia in contemporary clinical practice, by elucidating the complex relationships between CMD, stable angina and HFpEF [27].

4.2. Health disparities in HFpEF

Similar to CMD, disparate development of HFpEF has been seen in several distinct patient populations. Black individuals have a 50 % higher incidence of heart failure as compared to their White counterparts and have also been disproportionately impacted by chronic cardiometabolic conditions [28]. In regard to gender, studies have established that patients with HFpEF are more likely to be female [29]. With evolving data suggesting a correlation between HFpEF and CMD through a pro-inflammatory process, one must question the role social determinants of health and the psychosocial stressors may play, with need for future research.

5. Diagnostic assessment to work-up coronary microvascular dysfunction

Currently, there are no guidelines on the approach to assess CMD in HFpEF; however several different anatomical, invasive and noninvasive tests are utilized in the diagnostic evaluation of suspected CMD [6].

Factors influencing the limitations of various diagnostic techniques include cost, availability, reproducibility, accuracy, and prognostic validation through additional studies.

Noninvasive diagnosis of CMD involves various imaging techniques used to assess myocardial blood flow both at rest and during stress/hyperemia to measure microvascular resistance and CBF. Noninvasive diagnostic techniques are limited in their role to evaluate the non-endothelial dependent mechanism of CMD and include transthoracic echocardiography with doppler, positron emission tomography (PET), cardiac magnetic resonance (CMR), and computed tomography (CT) scans. Angiographic diagnostic techniques include coronary CT angiography, intracoronary temperature-pressure wire, intracoronary doppler flow-pressure wire, and complement endothelial-dependent evaluation which can be performed safely only in the catheterization laboratory with intracoronary provocative testing often with the use of acetylcholine.

Cardiac PET imaging is regarded as the gold standard in non-invasive CMD evaluation. PET imaging protocol is used to assess coronary vasomotor function through measurements of regional and global myocardial blood flow (MBF) following the administration of a vasodilatory agent, often in the form of adenosine or regadenoson. Following the stress agent, perfusion imaging is collected to allow calculation of the myocardial perfusion reserve and MBF, with myocardial flow reserve (MFR) <2.0 mL/g/min the universally accepted cutoff for identifying CMD [10]. PET is regarded as the most accurate of the noninvasive imaging modalities and has been widely validated and reproduced with weaknesses found in regard to its limited availability and high cost [10].

Stress perfusion CMR is another integral component of a comprehensive CMD evaluation. CMR, which encompasses the assessment of ventricular function, stress and rest perfusion, as well as the identification of viability or myocardial infarction [30], by calculating myocardial perfusion reserve index (MPRI) with a threshold MPRI <1.4 has demonstrated a correlation with coronary flow reserve (CFR), an invasive coronary reactivity that is the gold standard, as determined by coronary catheterization [31]. CMR limitations include its lower accuracy, reproducibility, and validity as a prognosticating modality, as compared to PET. In addition, CMR is characteristically expensive and has similar availability to PET.

Transthoracic echocardiography with doppler generally focuses on the left anterior descending artery, offering a method for CFR measurement through the evaluation of coronary blood flow velocity at rest and during vasodilator stress. Though relatively inexpensive and widely available, its accuracy is operator dependent, thus generally less accurate and limited to downstream left anterior descending artery territories.

Dynamic Myocardial Perfusion CT, is a noninvasive technique for quantifying blood flow of both, macro- and micro- coronary territories. Similar to invasive studies, CT may be utilized to calculate CT angiographic-derived fractional flow reserve (FFR); however this modality still requires additional validating measures [11].

5.1. Functional coronary angiography to assess vasoreactivity

Functional invasive coronary angiography and vasoreactivity testing involves both intravascular imaging followed by pharmacologic testing of the native coronary system to evaluate for vasodilatory defects. Coronary reactivity can be measured with invasive testing of endothelial function using intracoronary infusion of acetylcholine which promotes the release of NO and endothelium dependent vasodilation followed by intracoronary administration of sodium nitroprusside or adenosine to assess endothelial independent functions [32].

Invasive coronary angiography represents yet another highly effective approach for the evaluation of patients with CMD. Using catheter-based techniques, various parameters are measured to offer a comprehensive diagnostic picture. These parameters include invasive coronary flow reserve (iCFR), index of microvascular resistance, FFR, instantaneous Wave-free Ratio, and wave intensity analysis.

Invasive coronary flow reserve entails the assessment of blood flow within the coronary arteries both at rest and during vasodilation. Detecting abnormal iCFR is a crucial diagnostic criterion for patients with microvascular angina and is closely linked to an elevated risk of MACE [32]. This was best demonstrated in one of the large contemporary meta-analyses to discuss the prognostic value of CFR on MACE where it was found that in patients with isolated coronary microvascular dysfunction, an abnormal CFR was associated with a higher incidence of mortality (HR: 5.44, 95 % CI: 3.78–7.83) and MACE (HR: 3.56, 95 % CI: 2.14–5.90) [33].

Conversely, FFR is a distinctively different parameter calculated as the ratio between coronary pressure distal to a stenosis and aortic pressure during hyperemia. The use of FFR helps guide clinical decisions concerning coronary revascularization. This approach has been shown to reduce the incidence of cardiac events in comparison to relying solely on an anatomic strategy or adopting a conservative approach alone [10]. It is important to note that FFR is not primarily employed for measuring CMD, but rather serves as a tool to assess the severity of epicardial coronary artery stenosis [9]. As technology progresses, invasive simultaneous FFR, index of microcirculatory resistance, and CFR measurements could provide useful information regarding the proportion of contributions from epicardial disease versus CMD towards ischemia.

6. Therapeutic interventions for consideration in HFpEF associated with CMD

6.1. Pharmacologic treatment

There are presently no specific guidelines for the management of CMD in HFpEF. To date, the strongest evidence in support of treatment for CMD comes from the documented benefits of angiotensin-converting enzyme inhibitors (ACEI) in this population [31]. In a subset of women in the WISE study with microvascular dysfunction, randomization to therapy with quinapril for 16 weeks improved both CFR and symptoms as compared to placebo [34]. Additionally, given the strong link between inflammation and endothelial dysfunction, there has been data to support the benefit of high-intensity statin therapy by enhancing endothelial function and CFR, demonstrating their pleiotropic effects on inflammation and endothelial function[35]. Furthermore, there is data regarding mortality benefit of statins in the HFpEF population, likely due to the associated systemic proinflammatory state[36]. Beyond the effects of statins, other lipid modulating medications are currently under clinical trials including those addressing elevated Lp(a).

Similar to CMD, treatment for HFpEF has been largely centered around managing comorbidities such as hypertension, obesity, DM, along with atrial fibrillation and sleep apnea [37]. With this treatment strategy, the 1-year mortality rate for HFpEF patients post-hospitalization has been 36 % [6]. However, results from the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-preserved trial) showed a decrease in hospitalization, with meta-analyses showing a reduction in cardiovascular death in HFpEF patients taking sodium-glucose cotransporter-2 inhibitors. This was additive with the use of mineralocorticoid receptor antagonists and ACEI, angiotensin receptor blockers or angiotensin receptor-neprilysin inhibitors (ARNIs) [38,39]. A multicenter, prospective, randomized, blinded-outcome evaluating clinical trial called the Women's Ischemia Trial to Reduce Events in Non-obstructive CAD (WARRIOR) trial that is not restricted to patients with HFpEF, but evaluates women with INOCA looking at the use of such pharmacotherapy, to provide important data necessary to inform guidelines regarding how best to manage this growing and challenging population [40].

To date, the suggested treatment strategy for CMD overlaps with the traditional treatment of HFpEF and includes management of traditional

CVD risk factors, improving lifestyle and patient quality of life, and relieving anginal symptoms [12]. Given the emergence of additional pro-inflammatory, lifestyle, and socioeconomic risk factors, a comprehensive management that incorporates these factors is needed to combat CMD and prevent progression to cardiomyopathy.

As noted, ACEI and angiotensin receptor blockers function as vasodilators, countering the vasoconstriction produced through the influence of angiotensin II. Moreover, these medications are well known for mitigating the deleterious effects of hypertension on myocardial remodeling.

Newer medications, like SGLT-2 inhibitors, have demonstrated efficacy in improving coronary microvascular dysfunction linked to hyperglycemia as shown in the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG-OUTCOME) trial [39]. The Angiotensin-Neprilysin Inhibition in Patients With Mildly Reduced or Preserved Ejection Fraction and Worsening Heart Failure (PARAGLIDE-HF) study showed that the use of the ARNI, Sacubitril-Valsartan compared to Valsartan alone led to a greater reduction in plasma NT-proBNP levels, with trends in time to CV death, number and times of heart failure hospitalizations during follow-up, number and times of urgent heart failure visits during follow-up and time averaged proportional change in NT-proBNP [41]. In addition, the PROMIS-HFpEF study [42] provides crucial insights into HFpEF, particularly regarding gender disparities, as 55 % of its participants were women. The study is highly relevant to understanding CMD in HFpEF, shedding light on gender-specific mechanisms and outcomes in this population. It found that women with HFpEF exhibit distinct clinical and pathophysiological profiles compared to men, which may inform more tailored treatment strategies. The findings of the PROMIS-HFpEF study underscore the need to consider gender differences in the management of HFpEF, emphasizing the importance of further research in this area.

A systematic review and meta-analysis of 25 randomized controlled trials (RCTs)[43] has provided strong evidence supporting the use of beta-blockers in patients with heart failure and a left ventricular ejection fraction (LVEF) $\geq$40 %. The analysis demonstrated that beta-blocker therapy significantly reduces both all-cause and cardiovascular mortality in this patient population. These findings underscore the importance of beta-blockers as a cornerstone of heart failure treatment in individuals with preserved or mildly reduced ejection fraction.

With a higher presence of atherosclerosis in patients with CMD, antiplatelet therapy is essential [12]. Aspirin is the first-line antiplatelet therapy while P2Y12 platelet inhibitors can also be considered depending on associated conditions. To alleviate CMD symptoms such as angina, beta-blockers and short-acting nitrates are often prescribed. However, when combating CMD induced epicardial vasospasm, non-dihydropyridine calcium channel blockers are first-line treatment [12].

6.2. *Non-pharmacologic treatments*

Lifestyle interventions are fundamental in managing CMD and HFpEF, serving as the first line of treatment for all chronic CVDs. In HFpEF, characterized by metabolic derangements and systemic inflammation, lifestyle modifications such as dietary changes, regular physical activity, and weight management are essential. These interventions target the underlying mechanisms of HFpEF, improving symptoms and potentially reducing hospitalizations. A recent review [44] emphasizes the importance of tailored lifestyle interventions in HFpEF management, such as such as sodium restriction, plant-based diets, and structured aerobic exercises, which have been shown to improve functional capacity and reduce symptoms. Similarly, CMD, benefits from lifestyle measures. Addressing risk factors such as hypertension, diabetes, and hyperlipidemia through lifestyle changes can improve coronary microvascular function. A comprehensive review[45] discusses the pathogenic role of CMD across various cardiovascular conditions and underscores the significance of lifestyle modifications in its management. Key recommendations include weight management, increased physical activity, and a heart-healthy diet rich in antioxidants and anti-inflammatory foods. A comprehensive review of CMD emphasizes the role of these measures in enhancing endothelial function and reducing oxidative stress, which are crucial for managing the condition. It also highlights the importance of stress reduction techniques, as chronic stress can exacerbate CMD and related conditions.

Given the evidence linking a chronic proinflammatory state to the CMD contributing to HFpEF, medically tailored meals and food prescription programs may mitigate many of the diet-related comorbidities established as risk-factors[46] in the development of CMD and HFpEF alike. Exercise, specifically supervised exercise in the form of cardiac rehab programs, has been demonstrated to elicit a positive effect on endothelial function and arterial stiffness in HFpEF populations [47]. Implementing such lifestyle changes is crucial for all chronic CVDs, as these measures can modify disease progression, enhance quality of life, and reduce healthcare costs, highlighting the need for personalized approaches.

Beyond that, are enhanced external counterpulsation (EECP) treatment which is an FDA-approved, non-invasive therapy that involves applying external pressure cuffs to the lower extremities to increase coronary blood flow during diastole. In CMD, EECP can improve symptoms such as chest pain and shortness of breath by enhancing myocardial perfusion, oxygen delivery and ultimately CFR [48]. This therapy is particularly beneficial for patients with CMD who may not respond to conventional pharmacotherapy, offering a promising adjunctive treatment option to improve cardiovascular health and quality of life.

Emerging therapies such as coronary sinus reducer that is currently under evaluation in the COSIRA II trial[49] and the previously terminated CALADRIUS CD34+ stem cell trial[50] which was holding big promise in treatment of CMD by improving CFR, highlights how more large-scale studies are required before confirming these interventions can be first-line and/or adjuvant therapies in CMD treatment.

7. Conclusion

There is an increasing healthcare burden related to HFpEF and as such, an increasing need to clarify the role CMD plays in its development. To date, there are no guidelines for the prevention, evaluation, or treatment of CMD. Furthermore, there is a paucity of data including RCTs to demonstrate the direct pathophysiologic link between CMD and HFpEF. Risk factors for CMD are conventional risk factors including DM, obesity, hypertension, and hyperlipidemia, as well as autoimmune conditions associated with a chronic inflammatory state leading to endothelial dysfunction by way of impaired vasodilation of coronary microvasculature, decreased CBF, and ultimately, clinically significant CHF with preserved ejection fraction. There is a strong need for further studies and data to validate this hypothesis as a means of constructing a standardized approach to the evaluation and management of CMD and its role in the development of HFpEF. Fortunately, the current landscape of therapeutics for the treatment of HFpEF and CMD address an expansive terrain of targets, offering a hopeful perspective on future investigations.

Specific populations such as women and Black individuals are at an increased risk for the development of both, CMD and HFpEF, thus studies should be intentional with regard to participant recruitment in order to equitably improve health outcomes, with the goal to also assess the psychosocial stressors and lived experiences.

CRediT authorship contribution statement

Rachel M Bond: Writing – review & editing, Writing – original draft, Validation, Resources, Project administration, Data curation, Conceptualization. **Kendra Ivy:** Writing – original draft, Supervision, Resources, Data curation, Conceptualization. **Tre'Cherie Crumbs:** Writing – original draft, Data curation, Conceptualization. **Vikram Purewal:**

Writing – original draft, Data curation, Conceptualization. **Samed Obang:** Writing – original draft, Data curation, Conceptualization. **Dan Inder S Sraow:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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