Untangling the pathophysiologic link between coronary microvascular dysfunction and heart failure with preserved ejection fraction

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Coronary microvascular disease (CMD), characterized by impaired coronary flow reserve (CFR), is a common finding in patients with stable angina. Impaired CFR, in the absence of obstructive coronary artery disease, is also present in up to 75% of patients with heart failure with preserved ejection fraction (HFpEF). Heart failure with preserved ejection fraction is a heterogeneous syndrome comprising distinct endotypes and it has been hypothesized that CMD lies at the centre of the pathogenesis of one such entity: the CMD–HFpEF endotype. This article provides a contemporary review of the pathophysiology underlying CMD, with a focus on the mechanistic link between CMD and HFpEF. We discuss the central role played by subendocardial ischaemia and impaired lusitropy in the development of CMD–HFpEF, as well as the clinical and research implications of the CMD–HFpEF mechanistic link. Future prospective follow-up studies detailing outcomes in patients with CMD and HFpEF are much needed to enhance our understanding of the pathological processes driving these conditions, which may lead to the development of physiology-stratified therapy to improve the quality of life and prognosis in these patients.
Keywords

Coronary microvascular disease • Coro

Graphical Abstract

Introduction

Up to half of patients with angina and non-obstructive coronary artery disease (NOCAD) have evidence of coronary microvascular disease (CMD). Coronary microvascular disease is defined as an abnormality in the microcirculation leading to an inadequate vasodila
tory response, or a pathological vasoconstrictive response, to physiological or pharmacological stress. Coronary microvascular disease can be due to endothelial and/or vascular smooth muscle (VSM) (endothelium-independent) dysfunction. Contemporary invasive tests used to diagnose CMD are based on assessing the ability of the microvasculature to augment blood flow in response to a vasodilator stimulus, i.e. the flow reserve. Endothelium-independent CMD is defined as a coronary flow reserve (CFR) of <2.5 in response to adenosine, whereas endothelium-dependent CMD is defined as acetylcholine flow reserve of <1.5 in response to acetylcholine. In the context of NOCAD, diminished CFR and/or acetylcholine flow reserve is associated with inducible ischaemia, impaired quality of life, and increased risk of adverse cardiovascular outcomes. There is emerging evidence linking coronary microvascular dysfunction to heart failure with preserved ejection fraction (HFpEF), with up to 75% of patients with HFpEF suffering from impaired CFR despite the absence of obstructive coronary artery disease. Heart failure with preserved ejection fraction is a heterogeneous syndrome.
characterized by exercise intolerance. The contemporary cognizance is that HFpEF, like NOCAD, is an umbrella term comprising distinct endotypes, each with disparate underlying pathophysiology, therapeutic targets, and prognosis. Coronary microvascular disease-related HFpEF (CMD–HFpEF) represents one distinct endotype (Figure 1). In this review article, we will discuss the mechanistic role played by CMD in the pathogenesis of CMD–HFpEF, including abnormalities in cardiac–coronary coupling, which underlie the intimate relationship between myocardial perfusion and diastolic function.

**Cardiac–coronary coupling**

Myocardial perfusion is dependent on CFR and the dynamic interaction between myocardium and microvasculature. As a result of the phasic compression and decompression of intramyocardial vessels, coronary flow is intimately linked to myocardial relaxation and contraction; this process is called cardiac–coronary coupling, which can be readily characterized by coronary wave intensity analysis. Wave intensity analysis defines the nature (accelerating or decelerating flow) and origin (aortic, designated as forward, or microcirculatory, designated as backward) of energy fluxes that govern coronary blood flow (CBF). The backward expansion wave (BEW) is the main driver of flow in the healthy heart and it is secondary to decompression of the microvasculature in early diastole. Therefore, it is directly related to the degree of ventricular relaxation (lusitropy). The other major accelerating wave is the forward compression wave, which corresponds to the rise in aortic pressure after the aortic valve opens in early systole. The major decelerating wave is the backward compression wave (BCW), which arises during isovolumetric contraction. The relative balance of these wave energies is encapsulated in perfusion efficiency, which is the proportion of accelerating energy in relation to total energy flux; perfusion efficiency increases with exercise and pharmacologically induced microvascular dilation in health. In contrast, perfusion efficiency decreases with both exercise and pharmacologically induced microvascular dilation in CMD, primarily driven by attenuation of the accelerating BEW and accentuation of the decelerating BCW during exercise. Attenuation of the BEW during exercise can result from impaired lusitropy and a diastolic dysfunction phenotype that manifests during higher workloads, with resultant subendocardial ischaemia. Alternatively, subendocardial ischaemia during exercise may precipitate ischaemia-induced diastolic dysfunction, with diminished lusitropy subsequently impairing coronary perfusion further and resulting in an ischaemic cascade. As coronary flow is intimately linked with myocardial relaxation (and contraction), it can be challenging to ascertain causality between ischaemia and diastolic dysfunction.

Impaired ventricular relaxation has an adverse impact on coronary flow. In a coronary Doppler study of patients with unobstructed

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**Figure 1** This figure illustrates that heart failure with preserved ejection fraction is a heterogeneous syndrome comprising distinct endotypes, each with disparate underlying pathophysiology, therapeutic options, and outcomes. Patients can be characterized clinically according to factors such as pathophysiology (A), or they can be characterized using artificial intelligence-derived clusters that groups patients according to their clinical characteristics and clinical outcomes (B). Note: (B) is illustrative and not based on real data. CMD, coronary microvascular disease; HFpEF, heart failure with preserved ejection fraction.
coronary arteries and either normal left ventricular (LV) function or a cardiomyopathic process, early diastolic coronary flow at rest and CFR were attenuated in those with abnormal LV relaxation. Diastolic coronary flow was further reduced with an increase in heart rate in patients with impaired LV relaxation at rest.\(^1\)

These concepts underpin the intimate relationship between coronary flow and ventricular relaxation state (Figure 2). Alteration of this relationship lies at the forefront of the CMD–HFpEF pathophysiology. This will be discussed in more detail later in the review article.

**Figure 2** The left panel represents a normal control: the backward expansion wave becomes augmented on exertion, indicating enhanced lusitropy and myocardial perfusion. The right panel represents a patient with coronary microvascular disease: The backward compression wave indicates deceleration of flow and is augmented during exertion in these patients, whereas the backward expansion wave is attenuated. Note that diastole is defined electrically and all haemodynamic traces are gated to the R wave. The traces of aortic pressure, coronary pressure, and flow velocity are ensemble-averaged waveforms in a single calibrated wave. The wave intensity values (W/m\(^2\)/s\(^2\)) are for illustration purposes only and do not represent real data. The transthoracic echocardiogram-derived Doppler traces demonstrate normal left ventricular diastolic function in a control patient and impaired left ventricular diastolic function in a patient with coronary microvascular disease. BCW, backward compression wave; BEW, backward expansion wave; FCW, forward compression wave; FEW, forward expansion wave; LV, left ventricular; TTE, transthoracic echocardiogram.
Pathophysiologic link between coronary microvascular dysfunction and HFpEF

**Pathophysiology of coronary microvascular disease**

Traditionally, CMD has been attributed to a combination of microvascular architectural changes (such as microvascular obstruction and rarefaction), endothelial dysfunction, and/or VSM dysfunction. Endothelial or VSM (endothelium-independent) dysfunction may lead to an attenuated vasodilatory or a pathological vasoconstrictive response to stimuli, leading to a blunted augmentation of, or reduction of, CBF in response to stress. This can cause a supply–demand mismatch, leading to myocardial ischaemia. The cellular mechanisms regulating microvascular tone are summarized in Figure 3. However, recent animal models and clinical physiology evaluations suggest that coronary microvascular dysfunction may be a heterogeneous condition comprising distinct entities that form part of a disease spectrum. Based on physiology assessment in the catheter laboratory, we have described the presence of two distinct CMD endotypes, termed 'structural CMD' and 'functional CMD'. Both endotypes display impaired augmentation of CBF in response to intravenous adenosine (CFR < 2.5). However, whilst patients with structural CMD have an elevated minimal microvascular resistance (MR) (which translates to reduced maximal CBF), patients with functional CMD have a normal minimal MR but an attenuated vasodilatory reserve as they have reduced tone at rest. The endotypes have a similar core phenotype, with both groups demonstrating high prevalence of inducible ischaemia and inefficient cardiac–coronary coupling during physical exercise, but their pathogenesis differs at the microvascular level.
Vascular tone is mediated by nitric oxide (NO), which is synthesized by NO synthase (NOS). Patients with functional CMD have heightened resting CBF and NOS activity, reflecting a near-maximal vasodilatory state at rest (reduced resting microvascular tone), leading to an attenuated vasodilatory capacity in response to physiological stress. Endothelial NOS (eNOS) is thought to maintain hyperaemic CBF in response to hypoxia and shear stress, whilst neuronal NOS (nNOS) is thought to maintain CBF at rest (at least in the healthy heart). The elevated resting CBF in patients with functional CMD could be due to up-regulation of nNOS either as an appropriate response to an increased myocardial oxygen demand at rest or due to disordered autoregulation. Conversely, patients with structural CMD have normal resting CBF but an impaired ability to augment CBF in response to physiological stress and diminished peripheral CBF in the later stages of the disease. Animal studies have corroborated the findings of elevated resting CBF being associated with coronary microvascular dysfunction and myocardial ischaemia. In a swine model, animals with CMD were found to have heightened resting CBF, with a correspondingly high basal myocardial oxygen consumption (MVO₂). The former meant that, despite maintaining their hyperaemic CBF, there was reduced CFR. As elevated MVO₂ could not be matched by augmenting blood flow (i.e. myocardial oxygen delivery), there was a reduction in lactate consumption indicating anaerobic metabolism, and therefore, ischaemia. The authors of this study suggested that the basal oxygen demand was elevated either due to a myocardial substrate shift towards fatty acid oxidation leading to a reduced phosphate:oxygen ratio and an increased oxygen consumption for adenosine triphosphate (ATP) production or that it was due to mitochondrial uncoupling leading to a reduction in the phosphate:oxygen ratio, thereby increasing oxygen consumption at any given level of cardiac work. Interestingly, in a cohort of 74 women with angina, unobstructed coronary arteries and impaired CFR, low basal CBF (measured indirectly as basal average peak velocity) was associated with higher LV end-diastolic pressure and impaired diastolic strain. There was no difference in cardiovascular risk factors or LV structure between women with low and high basal CBF. The authors concluded that low basal CBF is associated with worse myocardial performance and may eventually lead to heart failure. This cohort of patients demonstrated similar physiological properties as patients with structural CMD. These mechanistic and clinical studies suggest that coronary microvascular dysfunction may lie on a spectrum, with normal function at one end and CMD–HFpEF at the other.

Finally, whilst the NO pathway is central to the development of CMD, dysfunction of the endothelin-1 (ET-1) pathway has also been implicated. Endothelin-1 is a highly potent coronary arteriolar vasoconstrictor; this effect is mediated by activation of the G-protein coupled endothelin A receptors on VSM cells. A specific genetic allele, which is associated with higher serum ET-1 levels, impaired myocardial perfusion on cardiac magnetic resonance imaging and reduced exercise tolerance has been identified in patients with angina and CMD. This supports the role of ET-1 dysregulation in the pathogenesis of CMD, as well as the possibility of precision medicine using genetics to target the ET-1 pathway in patients with CMD.

Pathophysiological links between coronary microvascular disease and heart failure with preserved ejection fraction

Impaired lusitropy

Whilst the significance of impaired NO pathways is well established in the development of CMD, eNOS dysfunction is also thought to play a central role in the pathogenesis of HFpEF. A systemic inflammatory state, induced by cardiovascular risk factors, leads to increased endothelial production of reactive oxygen species. Reactive oxygen species, such as superoxide ions, react with NO to form peroxynitrite. Peroxynitrite oxidizes the eNOS cofactor tetrahydrobiopterin (BH₄), which results in eNOS uncoupling and reduced NO production and bioavailability, which, in turn, leads to reduced cyclic guanosine monophosphate (cGMP) and protein kinase G (PKG) activity. Protein kinase G is involved in titin phosphorylation; titin is a cytoskeletal protein that acts as a bidirectional spring and is responsible for early diastolic recoil and late diastolic distensibility of cardiomyocytes. Therefore, titin hypophosphorylation makes cardiomyocytes less compliant. The impaired NO–cGMP–PKG axis leads to heightened diastolic stiffness through hypophosphorylation of titin in cardiomyocytes, leading to impaired lusitropy and LV diastolic reserve (Graphical Abstract).

Furthermore, an up-regulation of inducible nitric oxide synthase (iNOS) has also been implicated in the pathogenesis of HFpEF. Pharmacological eNOS inhibition, in a murine model of HFpEF, enhanced iNOS activity. This led to dysregulation of protein quality control, resulting in accumulation of misfolded proteins, which ultimately resulted in cardiomyocyte dysfunction and impaired lusitropy. Importantly, pharmacological inhibition of iNOS improved lusitropy and exercise intolerance in this model of HFpEF.
**Subendocardial ischaemia**

Mechanistic studies have consistently demonstrated that patients with HFrEF have an inability to adequately augment their myocardial blood flow (MBF) and oxygen delivery during stress. Patients with HFrEF and NOCAD demonstrate a higher LV external work, MVO₂ and MBF at rest but blunted rise in these indices during dobutamine-induced stress, compared to control subjects. Although myocardial oxygen extraction is enhanced, the rise in MBF (supply) is inadequate to meet the change in LV external work (demand) in patients with HFrEF. The myocardial oxygen supply-demand mismatch is associated with limitations in LV systolic and diastolic reserve, alongside the inability to adequately increase cardiac output during exercise, which can lead to sufficient ischaemia to cause elevation in high-sensitivity troponin T levels. Patients with HFrEF have reduced phospho-creatine:ATP ratio during exercise, which may explain the impaired LV diastolic reserve as ATP is required for diastolic relaxation. This may potentiate ischaemia due to attenuated augmentation of MBF during stress, may be pathogenic in HFrEF, it is not clear whether this precedes the changes in myocardial reserve or is caused by the latter. A vicious cycle has been proposed, whereby attenuated oxygen delivery impar myocyte relaxation, which promotes heighten ed myocardial tension and increased oxygen consumption demands.

In summary, cardiovascular risk factors, such as hypertension, diabetes mellitus, and hyperlipidaemia, lead to a systemic inflammatory state, which leads to endothelial dysfunction through eNOS uncoupling. Coronary endothelial dysfunction, clinically diagnosed as an inability to augment CBF by >50% in response to acetylcholine, leads to impaired lusitropy through the NO–cGMP–PKG pathway. Impaired lusitropy may potentiate subendocardial ischaemia, both leading to impaired myocardial reserve and HFrEF. Coronary microvascular disease, which may represent a later stage in the coronary microvascular dysfunction spectrum than endothelial dysfunction, leads to subendocardial ischaemia through the impaired ability of the VSM to relax in response to appropriate stimuli. This may potentiate impaired lusitropy and lead to impaired myocardial reserve and HFrEF (Graphical abstract).

**Clinical links between coronary microvascular disease and heart failure with preserved ejection fraction**

Cardiovascular risk factors, such as hypertension, diabetes mellitus, hyperlipidaemia, and obesity, lead to a cascade of pro-inflammatory events that eventually lead to eNOS uncoupling and endothelial dysfunction. Hypertension has been implicated in the development of CMD. In addition to causing eNOS dysfunction, it leads to enhanced endothelin production resulting in inappropriate coronary endothelial vasoconstriction. Hypertension is also associated with architectural changes, such as capillary rarefaction, medial hypertrophy, and fibrosis of arteriolar vessels. These result in an inability of the coronary vasculature to augment its blood flow. Insulin resistance and hyperglycaemia, both cardinal features of diabetes mellitus, also alter coronary vascular tone regulation. Coronary microvascular disease is prevalent in patients with T2DM and studies have shown that impaired myocardial flow reserve is strongly associated with the degree of albuminuria in these patients. Coronary microvascular disease and albuminuria may, therefore, share common mechanisms related to the pathogenesis of diabetic micro-vasculopathy.

Women may be susceptible to coronary vasomotor disorders due to gender-specific risk factors, such as systemic inflammation and endocrine changes. During adulthood, men tend to have a higher inflammatory predisposition than women; however, this predilection swaps genders after menopause. Oestradiol is generally protective against inflammation and reduced oestrogen levels post-menopause are associated with altered vascular function, heightened systemic inflammation and up-regulation of the renin–angiotensin–aldosterone-one and sympathetic nervous systems. These have all been implicated in the pathogenesis of CMD and HFrEF and serve as the reasons for why women may be biologically more likely to develop CMD–HFrEF.

**Research and clinical implications**

**Research implications**

Impaired flow reserve, the hallmark of CMD, likely leads to impairment of myocardial reserve, which eventually results in HFrEF. Impaired CFR, as measured by the diminished response to adenosine and acetylcholine, has been closely linked to exertional pulmonary arterial wedge pressure in patients with HFrEF. Future research should prospectively assess the dynamic relationship between intra-coronary physiology and LV haemodynamics during exercise; this may help untangle the ‘cause vs. effect’ dilemma that currently plagues our understanding of this intimate relationship. Along with human studies, animal HFrEF models (for instance, using Dahl salt-sensitive rats) may also be useful to understand the longitudinal pathophysiological link between CMD and HFrEF. Once a mechanistic link has been confirmed, the next step would be development of pharmacotherapy targeting specific abnormalities within the pathway. Although the recent ‘one size fits all’ therapeutic studies targeting the NO–cGMP–PKG pathway have yielded disappointing results, it is conceivable that better disease characterization and endotype-specific therapeutic targets may yield positive outcomes. Informatics and machine-learning techniques may help to identify different endotypes based on statistically clustered clinical and biological characteristics.

Furthermore, a better understanding of the mechanistic link between CMD and HFrEF may provide further therapeutic targets for the CMD–HFrEF endotype, which target the subendocardial ischaemia pathway. Finally, development of risk prediction scores, using invasive and non-invasive parameters of coronary microvascular function, may allow clinicians to predict the likelihood of patients developing CMD–HFrEF.
Figure 4 Results of therapeutic trials targeting the nitric oxide–cyclic Guanosine Monophosphate–protein kinase G pathway. (A) Summarizes the pilot data (or pre-clinical data), clinical trial data and the potential reasons for neutral outcomes, whilst (B) highlights the specific intracellular pathways that each of the novel agents act on. None of these trials met their primary endpoints. However, all of these trials are plagued by specific and generic trial design limitations. The treatment arm of CAPACITY-HFpEF and SOCRATES-PRESERVED trials lasted for only 12 weeks, which may not have been long enough to lead to sustained improvements in the study endpoints. The patient cohort recruited in the CAPACITY-HFpEF and VITALITY-HFpEF trials may represent a ‘healthier’ cohort that is not representative of the ‘real-world’ patient cohort. In the CAPACITY-HFpEF study, only 20% of patients had elevated filling pressures and a majority of patients had New York Heart Association II symptoms. Attenuation of cyclic Guanosine Monophosphate levels in patients with HFpEF is due to the loss of upstream nitric oxide rather than an excessive breakdown of cyclic Guanosine Monophosphate. It is, therefore, not unexpected that attempting to augment cyclic Guanosine Monophosphate by inhibiting its breakdown did not lead to clinically meaningful improvements in patients’ haemodynamics or exercise capacity in the RELAX trial. Furthermore, whilst the agents used in these trials target the nitric oxide–cyclic Guanosine Monophosphate–protein kinase G pathway, none of the trials directly studied physiological endpoints of impaired vascular function, such as peripheral or coronary endothelial function. Additionally, the physical functioning endpoints (6-min walk distance and change in peak VO\textsubscript{2}) may not be able to discriminate among effective therapies because patients with HFpEF usually suffer from multiple comorbidities and their impaired physical functioning may be multifactorial in nature. BP, blood pressure; cGMP, cyclic Guanosine Monophosphate; DM, diabetes mellitus; GTP, Guanosine Triphosphate; HFpEF, heart failure with preserved ejection fraction; HTN, hypertension; KCCQ, Kansas City Cardiomyopathy Questionnaire; LAV, left atrial volume; NO, nitric oxide; PA, pulmonary artery; PKG, protein kinase G; sGC, soluble Guanylate Cy clase; 6MWD, 6-min walk distance.
Clinical implications

Once the diagnosis of CMD has been confirmed, aggressive pharmacotherapy should be commenced with the primary aim of ameliorating microvascular dysfunction and the secondary aim of preventing, or delaying, the onset of CMD–HFpEF. Small studies have demonstrated improvement of CFR with angiotensin converting enzyme inhibitors and statins. Longitudinal studies are needed to assess whether this treatment strategy prevents the development of HFpEF in patients with CMD. To this effect, routine non-invasive monitoring of systemic microvascular function, via peripheral endothelial assessment or non-invasive coronary flow velocity reserve measurement, may permit focused titration of prognostic and anti-ischaemic therapy in patients with CMD.

After the disappointing results of renin–angiotensin–aldosterone system inhibitors and beta-blockers in patients with HFpEF, the scientific community turned to agents that could modulate the NO–cGMP–PKG pathway. However, despite initial positive outcomes from pre-clinical and pilot studies, none of these drugs have demonstrated favourable outcomes in large trials. The study results and the potential reasons behind the neutral outcomes are illustrated in Figure 4.

It is now increasingly recognized that HFpEF is a heterogeneous condition comprising distinct endotypes, which have vastly disparate underlying pathophysiology. Therefore, a ‘one size fits all’ approach is unlikely to yield positive therapeutic outcomes. Coronary microvascular disease–HFpEF is a distinct HFpEF endotype, with impaired CFR and ensuing subendocardial ischaemia and impaired lusitropy being at the centre of its pathogenesis. None of the aforementioned therapeutic trials reported patients’ flow reserve (in response to adenosine or acetylcholine) or stipulated an impaired flow reserve in their inclusion criteria. Therefore, it is conceivable that a large percentage of patients recruited in these studies did not have the CMD–HFpEF endotype. Furthermore, although the agents used in these trials theoretically potentiate the NO–cGMP–PKG pathway, none of them ameliorate the subendocardial ischaemia that is fundamental to the development of CMD–HFpEF. Future therapeutic studies should trial endotype-specific agents to target the underlying pathological pathways.

Finally, long-term follow-up of patients with CMD–HFpEF is required to track the natural trajectory of this disease process. Figure 5 summarizes the future research and clinical implications of the CMD–HFpEF mechanistic link.

Conclusion

Coronary microvascular disease–HFpEF may be a distinct HFpEF endotype with coronary microvascular dysfunction being the underlying mechanism leading to impaired myocardial reserve. We have scrutinized the role of subendocardial ischaemia and impaired lusitropy in the development of CMD–HFpEF and have explored the challenges in demonstrating causality between CMD and HFpEF. We have also discussed the role of gender in CMD–HFpEF and have explored the limitations of the contemporary HFpEF therapeutic trials targeting the NO–cGMP–PKG pathway. Further longitudinal and mechanistic studies are required to verify the proposed mechanistic link between CMD and HFpEF. A better understanding of the...
common pathophysiology may pave the way for the development of therapeutic agents that can improve these patients’ quality of life and cardiovascular outcomes.

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