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The role of coronary microvascular dysfunction in the pathogenesis of heart failure with preserved ejection fraction☆

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ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) is a common condition with few effective therapies and hence represents a major healthcare burden. The clinical syndrome of HFpEF can be caused by varying pathophysiological processes, with coronary microvascular dysfunction (CMD) proposed as one of the aetiologies, although confirming causality has been challenging. CMD is characterised by the inability of the coronary vasculature to augment blood flow in response to a physiological stressor and has been established as the driver of angina in patients with non-obstructed coronaries (ANOCA), and this has subsequently led to efficacious endotype-directed therapies. CMD is also highly prevalent among sufferers of HFpEF and may represent a novel treatment target for this particular endotype of this condition. This review aims to discuss the role of the microcirculation in the healthy heart how it's dysfunction may precipitate HFpEF and explore the current diagnostic tools available. We also discuss the gaps in evidence and where we believe future research should be focussed.

1. Introduction

The advent of selective coronary angiography proved a boon for the investigation of angina, helping diagnose ischaemia secondary to epicardial coronary obstruction [1]. However, even in the early days of angiography, a sizable proportion of patients with cardiac-sounding chest pain were found to have unobstructed coronary arteries; modern registries corroborate this observation with approximately 50 % of angina sufferers found to have unobstructed coronary arteries [2]. Such patients were historically said to suffer from 'Cardiac Syndrome X', an anachronism reflecting the ill-defined nature of this condition, the more contemporary description of this population is patients with angina and nonobstructive coronary arteries (ANOCA). Despite early studies describing generally positive outcomes comparable to the general population in this syndrome [3], modern registries have conversely identified outcomes that are far from benign. Several theories surrounding its pathophysiology were purported, including psychosomatic [4] but, despite the initial lack of understanding, coronary microvascular dysfunction (CMD) was proposed as a potential cause for these symptoms as far back as the 1960's [5]. Among the heterogenous ANOCA population, those with confirmed CMD have an increased risk of major adverse cardiovascular events (MACE) [6]. CMD arises from an impaired vasodilatory (or even paradoxically vasoconstrictory) response precipitating demonstrable ischaemia. The development of in vivo techniques to interrogate the coronary microcirculation in patients with ANOCA has enabled a more granular understanding of the underlying disease mechanisms. Physiological stratification of patients with ANOCA enables prognostication and the ability to predict response to therapy [7–10].

Akin to historical Syndrome X, heart failure with preserved ejection fraction (HFpEF) is pathophysiologically ill-defined and lacks effective treatments; subsequently, particular interest is now being paid to a proposed pathophysiological link between it and CMD [11]. Identifying this mechanistic link, and better characterising the heterogenous HFpEF population may similarly usher in effective endotype-derived therapies. This review article will discuss the evolving mechanistic link between CMD and HFpEF, the diagnostic tools available to characterise it, and the current gaps in knowledge.

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2. The role of the coronary microcirculation

As the resting coronary arteriovenous oxygen difference is near maximal [12], with minimal change on exertion, myocardial perfusion is largely determined by coronary blood flow (CBF) [13]. CBF is driven by the pressure difference between the aortic and coronary sinus, which is modulated both by microvascular resistance downstream as well as the dynamic interaction between the myocardium and microcirculation (Fig. 1) [14]. The large epicardial arteries act as conduits offering minimal resistance, with the majority of coronary vascular resistance generated further down the vascular bed by pre-arterioles, arterioles and capillaries, designating them as important regulatory components of coronary flow [12,15].

Equally, phasic compression and decompression of the myocardium surrounding the coronary vasculature determines coronary haemodynamics, with this intimate and unique relationship termed 'cardiac-coronary' coupling. This is evident using wave intensity analysis (WIA), a valuable invasive physiological tool adapted from the study of gas dynamics that quantifies flow and pressure within a fluid system. During the cardiac cycle, energy fluxes governing blood flow are defined based on their origin and vector; forward (proximal) and backward (distal) originating components are governed by aortic and myocardial forces respectively, whilst accelerative forces correspond with increases in flow and pressure (with the inverse being true for decelerative forces) [16]. Coronary perfusion refers to the proportion of accelerating to decelerating wave energies; in the healthy heart, coronary perfusion efficiency increases on exertion. This is attenuated in disease states such as CMD, left ventricular hypertrophy and aortic stenosis [9,17–20]. Within the various dominant waves observed throughout the cardiac cycle, CBF peaks during diastole with the 'backwards expansion' wave (BEW), a distal, accelerating force originating from decompression of the microvasculature [20]. Resultantly, the magnitude of the BEW is directly related to ventricular lusitropy [11].

3. Coronary microvascular dysfunction

Prior to the contemporary association with CMD, ANOCA had been managed empirically with patients left either falsely reassured or with ongoing symptoms. The CorMicA Study demonstrated that the clinician's knowledge of the ANOCA endotype, yielded improved patient symptom scores, but the precise mechanism behind this remained unclear [11]. CMD is diagnosed invasively by an impaired vasodilatory response to a pharmacological stressor, termed reduced coronary flow reserve (CFR) [21]. CFR is the most widely used clinical tool with diminished values associated with poorer clinical outcomes [22]. The ChaMP-CMD study identified that only patients with a reduced CFR benefit from anti-anginal therapy, supporting the role for endotype directed therapy. CMD can be further stratified into functional or structural endotypes representing distinct systemic pathobiological dysfunctional states but with similarly high rates of MACE [25]. Structural CMD is characterised by the inability of the microcirculation to dilate in response to stress (elevated minimal microvascular resistance) and could be related to capillary rarefaction or myocardial fibrosis. Conversely, functional CMD is characterised by heightened vasodilatation at rest, limiting flow augmentation in response to a stressor, despite normal minimal microvascular resistance without obvious architectural changes in the vasculature. Both endotypes are associated with systemic nitric oxide synthase dysfunction and studies are currently being undertaken to assess if they respond differently to targeted pharmacotherapy.

Mechanistic work defining the ANOCA population ultimately helped facilitate endotype directed therapies, leading to quantifiable benefits. Considering the heterogenous nature of HFpEF, advancements in our understanding of it may prove analogous to the ANOCA narrative.

4. Mechanistic link between coronary microvascular dysfunction and heart failure with preserve ejection fraction

4.1. Association

Heart failure with preserved ejection fraction (HFpEF) is a heterogenous syndrome characterised by insufficient forward flow despite a maintained left ventricular (LV) ejection fraction. The pathophysiological hallmark of this condition is impaired lusitropy, redistributing left ventricular filling from early to late diastole and in-turn precipitating marked exercise intolerance. CMD has been proposed as a cause for a subset of HFpEF sufferers owing to high rates of CMD observed among HFpEF sufferers in the previous literature; demonstrated invasively by a

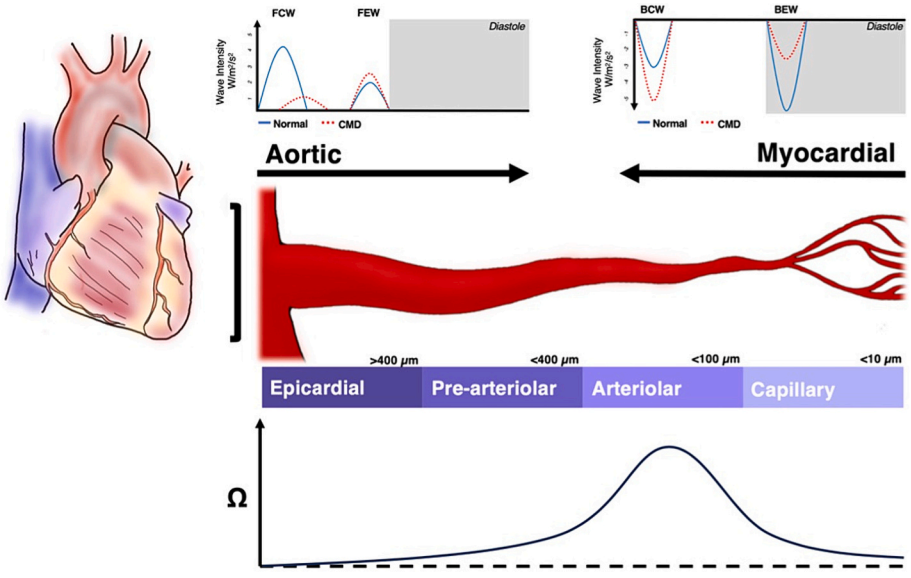

Fig. 1. The coronary circulation from epicardial to arteriole level with their contribution to conductance below. Wave energies are represented above, based on whether they are forward or backward originating, and based on either normal physiology (blue line) or CMD (red-hatched line). Notably, the backwards expansion wave (BEW), is markedly reduced in intensity in CMD; the BEW represents a backwards suction force on decompression of the microvasculature during diastole. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

diminished CFR [23,24], non-invasively by reduced myocardial perfusion reserve on cardiac MRI [25], and histologically as marked coronary microvascular rarefaction [26]. Of note, in the PROMIS-HFpEF study, reduced CFR was not only associated with markers of heart failure severity (such as right ventricular dysfunction and raised natriuretic peptide measurements), but also systemic endothelial dysfunction, alluding to the pro- inflammatory paradigm [27]. Notably, the presence of CMD in HFpEF sufferers portends a worse prognosis, with a >5 times increased risk of related hospitalisation and MACE [28]. Recent invasive data assessing coronary blood flow in a small group of HFpEF sufferers, with objective CMD, identified a blunted coronary microvascular response amid a marked increased in microvascular resistance, suggesting an underlying structural CMD phenotype [29]. However, elements of both functional and structural CMD endotypes are present in HFpEF, with a reduced CFR being secondary to both high resting CBF as well as poor vasodilatory capacity [21]. This lends credence to suggestions that CMD is a natural precursor to some forms of HFpEF [28]. Whilst this association does not provide a causal link in of itself, CMD has been purported to cause HFpEF by the following mechanisms (Fig. 2).

4.1.1. *Systemic pro-inflammatory state*

Much like CMD, endothelial dysfunction is purported to play a central role in the development of HFpEF [27,30]. Amid multiple pro-inflammatory comorbidities (such as diabetes mellitus, hypertension and obesity) and increased haemodynamic load, dysfunctional coronary endothelium produces reactive oxygen species which react with nitric oxide (NO) to form peryoxynitrite. The subsequent oxidative stress from peroxynitrite triggers endothelial nitrix oxide synthase (eNOS) uncoupling, reducing NO bioavailability. This in turn leads to reduced cyclic guanosine monophosphate (cGMP) and protein kinase G (PKG) activity. Ultimately impairment of the NO-cGMP-PKG pathway, involved in hypo-phosphorylation of the titin cytoskeletal protein, leads to reduced diastolic distensibility and subsequent impaired lusitropy. Increased metabolic and haemodynamic load also lead to other pro-inflammatory and pro-fibrotic changes precipitating negative lusitropy, such as deposition of less compliant collagen types in the myocardial extracellular matrix and impaired collagen homeostasis [30]. Notably, CMD is highly prevalent in inflammatory rheumatological conditions, with pro-inflammatory mediators also reducing NO bioavailability [31], lending further credence to this association amid an inflammatory state.

4.1.2. *Subendocardial ischaemia*

As the most distal layer served by the coronary circulation, the subendocardium is particularly vulnerable to ischaemia, owing to epicardial factors affecting conductance downstream, as well as high extravascular pressure [32]. This is likely exacerbated in HFpEF, as there is a significant reduction in myocardial energy reserves, as evidenced by a reduced phosphocreatine to ATP ratio [33], leading to reduced availability of ATP. This attenuates diastolic relaxation due to increased cross-bridge cycling, reducing cardiac output which in turn further impairs coronary perfusion, precipitating a vicious ischaemic cascade [11]. Either separately, or in tandem, shear stress mediated eNOS dysfunction may also promote ischaemia. Subsequent repetitive myocardial injury may precipitate fibrosis long term, with raised resting LV pressures as a corollary. This may represent a continuum of CMD endotypes in the development of HFpEF, whereby functional CMD precipitates subendocardial ischaemia, and the ensuing architectural changes commit the sufferer to structural CMD, but longitudinal data to support this hypothesis are lacking at present.

4.2. *CMD as a by-product of HFpEF*

Impaired lusitropy and subendocardial ischaemia are cardinal features of HFpEF but, as they are intrinsically linked, delineating one from the other remains difficult [34]. Subsequently, proposing CMD as a causal element of HFpEF remains tenuous, as impaired coronary blood flow may be explained as a secondary feature of adverse LV remodelling; for instance, Claridge et al. previously identified that coronary blood flow increased with enhanced cardiac contractility [35], highlighting the mechanistic relationship between LV haemodynamics and coronary flow. Conversely, augmenting coronary flow in that study cohort did not primarily affect LV contractility. In addition, other doppler studies have identified attenuated early diastolic coronary flow and CFR secondary to negative lusitropy [11].

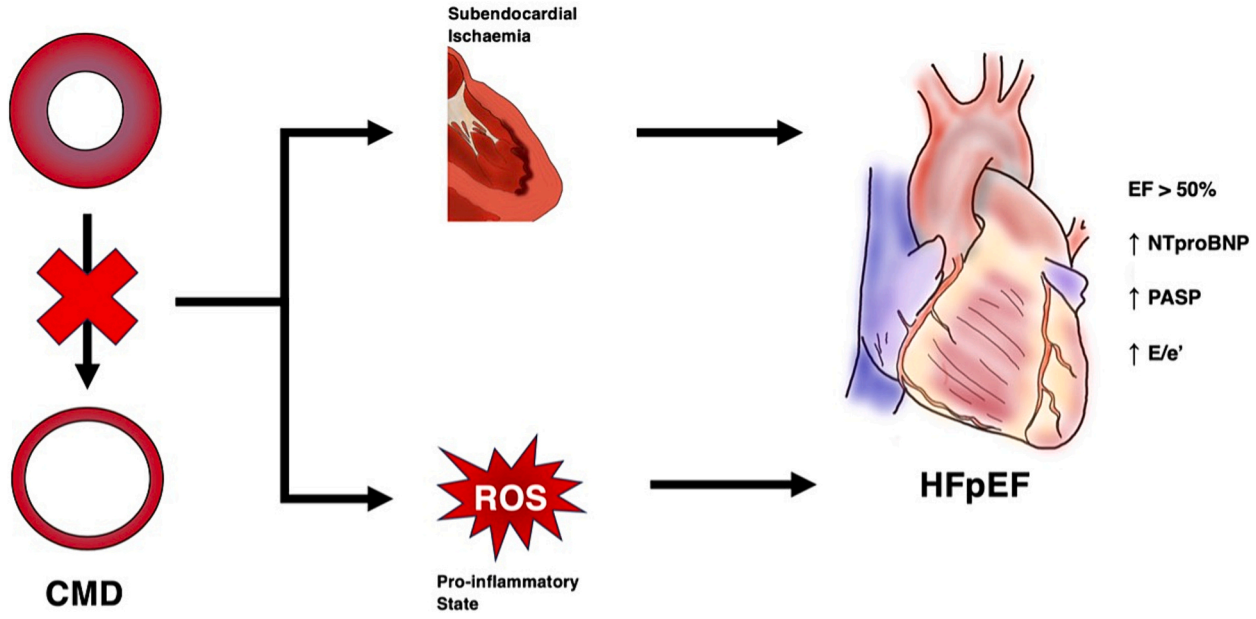

Fig. 2. The proposed continuum between CMD and HFpEF via two mechanisms; CMD can precipitate HFpEF via diffuse subendocardial ischaemia, as well as by reduced NO bioavailability amid a pro-inflammatory state.

5. Current diagnostic tools

5.1. Diagnostic challenges in HFpEF

Diagnosing HFpEF from an undifferentiated presentation of dyspnoea can prove challenging, owing to indeterminate diagnostic criteria within a poorly defined patient group. European society guidance suggests the use of pragmatic risk scores such as 'H2FPEF' and 'HFA-PEFF' but makes note of their variable diagnostic performance [36], with results often being discordant. A more detailed consensus statement from the Heart Failure Association proposes an advanced algorithm with an invasive assessment arm, but this is limited to left ventricular end-diastolic and pulmonary capillary wedge pressure measurements offering limited insight into underlying pathophysiological mechanisms [37]. Furthermore, in some HFpEF sufferers, left sided pressures may only increase on exertion [36], but it is often not practicable to perform invasive exercise testing in all candidates.

Ultimately, the contemporary diagnosis of HFpEF describes a clinical syndrome that may result from multiple potential aetiologies. There is evidence of differing treatment outcomes, albeit tenuous, in different phenotypes identified with artificial intelligence (by grouping demographic and clinical characteristics) [38]. Whether pathophysiological endotyping could lead to targeted therapies that are more effective is unkown at present.

5.2. Diagnosing CMD in HFpEF

Invasive microcirculatory function testing is important in the comprehensive assessment of CMD, both in delineating its' presence as well as establishing an underlying endotype [39]. One such tool is measuring CFR, which is a validated hyperaemic index for delineating endothelial-independent CMD, and its' use has proven benefits in tailoring therapies [8,10]. As alluded to earlier, CFR is defined as the ratio between maximal coronary blood flow during hyperaemia versus baseline; in the normal coronary circulation, coronary blood flow should markedly increase with stress, but this response is blunted in individuals with microcirculatory dysfunction due to the variety of aforementioned factors [40]. Despite the increasing ubiquity of coronary physiology testing for epicardial coronary disease (including fractional flow reserve), microcirculatory function testing remains limited in standard practice throughout U.K. cardiac catheter laboratories [40]. Whilst CFR measurements are useful in diagnosing and treating CMD, it's relevance beyond diagnosis in HFpEF remains unknown and it is far from being a common part of the HFpEF work-up with further work required to determine whether it remains a unique therapeutic target within this cohort.

Whilst invasive coronary physiology may help unravel the link between CMD and HFpEF, non-invasive testing stands to be the practical choice for diagnosis and monitoring; identifying non-invasive correlates could therefore promote the widespread application of endotype derived therapies for HFpEF. Quantitative perfusion cardiac magnetic resonance imaging (CMR) is well placed in this regard, owing to it's high accuracy at detecting CMD among the ANOCA cohort when compared against the invasive gold standard [41]. Myocardial perfusion reserve (MPR), akin to CFR, is a quantitative marker used in CMR that compares myocardial blood flow at hyperaemia versus rest, with diminished values indicative of CMD. High rates of CMD have also been identified via perfusion CMR in the HFpEF population akin to similar invasive studies. Notably, markers of CMD did not correlate with those found to have myocardial fibrosis, potentially alluding to phenotypic differences within the heterogenous HFpEF population [25]. Stress echocardiography also has diagnostic utility in HFpEF, demonstrating inadequate augmentation of cardiac output on exertion by increased LV filling and pulmonary artery systolic pressures; however, it is poorly sensitive and cannot exclude HFpEF [37]. Recently, exercise ECG has demonstrated high specificity for identifying an underlying ischaemic substrate among INOCA patients, however this requires validation in a HFpEF population [42].

6. Implications and future work

As the burden of HFpEF remains an unmet health need, better characterisation of this patient population may hold the key to effective endotype-directed therapies. However, whilst rudimentary attempts at subtyping HFpEF based on microvascular function have been performed previously [34,43], establishing CMD as a causal element remains difficult, particularly as impaired coronary blood flow may be explained as a secondary feature of adverse LV remodelling, impairing capillary distensibility. Despite the aforementioned association between impaired CFR and HFpEF earlier in this review article, the mechanistic link between CMD and HFpEF remains tenuous [44].

This hurdle may be overcome in several ways. Developing well-defined registries of HFpEF patients with rich invasive, non-invasive and demographic data can help tease out more consistent phenotypic groups. In addition, characterising the presence of CMD and/or underlying endotypes in HFpEF sufferers can help identify disparate outcomes in this patient group, as well as study the role of directed therapies. Follow up of richly characterised CMD registries may also identify changes preceding HFpEF, helping to establish a temporal association. Further mechanistic work can then explore the proposed causal link between CMD and HFpEF in an enriched study population, perhaps by investigating the acute temporal relationship between changes in coronary physiology and LV contractility in this group.

7. Conclusion

HFpEF remains ill-defined, sub-optimally treated, and burdensome internationally. The advent of coronary physiology revolutionised the management of ANOCA, eventually helping to establish endotype-derived therapies; HFpEF stands to similarly benefit via further mechanistic work and better-defined patient registries for accurate phenotyping. CMD is highly prevalent among HFpEF sufferers and may represent a pathophysiological mechanism. Elucidating the association between HFpEF and CMD may be the start of identifying novel therapeutic targets to help alleviate this public health need.

Ethical statement

This study did not require ethics committee approval due to its nature as a review article. This article is the sole, original work of the named authors.

CRediT authorship contribution statement

Becker Al-Khayatt: Writing – original draft. **Divaka Perera:** Supervision, Conceptualization. **Haseeb Rahman:** Writing – review & editing, Supervision.

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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