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SPOTLIGHT REVIEW

The pathogenic role of coronary microvascular dysfunction in the setting of other cardiac or systemic conditions

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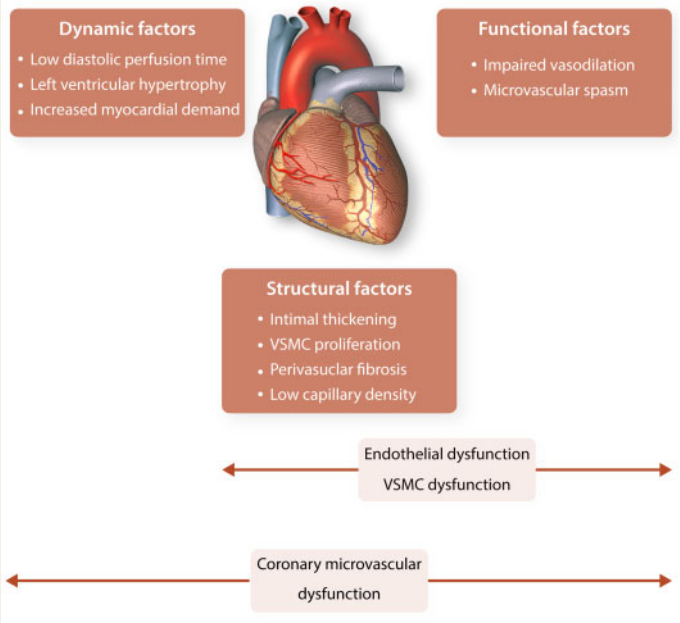
Abstract

Coronary microvascular dysfunction (CMD) plays a pathogenic role in cardiac and systemic conditions other than microvascular angina. In this review, we provide an overview of the pathogenic role of CMD in the setting of diabetes mellitus, obesity, hypertensive pregnancy disorders, chronic inflammatory and autoimmune rheumatic disorders, chronic kidney disease, hypertrophic cardiomyopathy, and aortic valve stenosis. In these various conditions, CMD results from different structural, functional, and/or dynamic alterations in the coronary microcirculation associated with the primary disease process. CMD is often detectable very early in the course of the primary disease, before clinical symptoms or signs of myocardial ischaemia are present, and it portrays an increased risk for cardiovascular events.

Graphical Abstract



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This article is part of the Spotlight Issue on Coronary Microvascular Dysfunction.

1. Introduction

Microvascular angina (MVA) is a form of ischaemic heart disease (IHD) characterized by signs and symptoms of cardiac ischaemia triggered by coronary microvascular dysfunction (CMD).[1] CMD, however, can also occur and play a pathogenic role in cardiac conditions other than MVA, i.e. hypertrophic cardiomyopathy (HCM) and aortic valve stenosis (AoS) which are also referred to as type 2 CMD.[2] Moreover, CMD can be present in systemic conditions such as diabetes mellitus (DM), obesity, hypertensive pregnancy disorders (HPD), chronic inflammatory and autoimmune rheumatic disorders, and chronic kidney disease (CKD). Importantly, although CMD may not always cause symptoms of cardiac ischaemia in the setting of the cardiac and systemic conditions mentioned above, its presence has been shown to be consistently associated with adverse clinical outcomes.

This review provides an overview of the pathogenic role of CMD in the setting of cardiac and systemic conditions other than MVA, and its clinical implications. We will describe the functional role of the coronary microcirculation in the delivery of blood for myocardial perfusion, and discuss the different conditions associated with CMD.

2. The role of the microvasculature in the coronary circulation

In the coronary circulation, the resistance of the vascular components is coordinated by different regulatory mechanisms to match blood flow with oxygen requirements.[3,4] The large epicardial coronary arteries (500 μm-5 mm in diameter) as well as the capillaries and venules act mainly as conductance vessels and offer very little resistance. The coronary blood flow is mainly controlled by the pre-arterioles and arterioles, also called the microvasculature. The epicardial pre-arterioles (100-500 μm in diameter) serve to maintain pressure within narrow limits at the origin of the arterioles and respond to flow-related stimuli with endothelium-dependent vasoreactivity. The intramyocardial arterioles (<100 μm in diameter) have the highest resistance and respond either by myogenic control or metabolites, differing per size.[5] Myogenic control prevails in the medium-sized arterioles (40-100 μm in diameter), where stretch receptors in vascular smooth muscle cells (VSMCs) react to changes in pressure, high intraluminal pressure leads to vasoconstriction, and vice versa. Control by metabolites prevails in the smaller arterioles (<40 μm in diameter), in which an increased metabolic activity leads to vasodilatation. This leads to a reduction in pressure in the medium-sized arterioles, stimulating myogenic dilation, and a subsequent increased flow upstream resulting in endothelium-dependent vasodilation in the pre-arterioles and epicardial coronary arteries.

CMD can result in the inability of the coronary arteries to augment coronary blood flow (vasodilatory abnormality) and/or in a reduction in coronary blood flow (coronary microvascular spasm). CMD leading to ischaemia can occur in the absence and/or in the presence of obstructive epicardial coronary artery disease (CAD). CMD can be the consequence of an abnormal structure of the coronary microvasculature (e.g. intimal thickening, VSMC proliferation, low capillary density), a dynamic maldistribution of coronary blood flow often resulting from extracoronary causes (e.g. short diastolic perfusion time) or compressive forces generated in the myocardium, or an abnormal coronary function (e.g. impaired vasodilatation by endothelial dysfunction), as depicted in *Figure 1*.[6] Endothelial dysfunction is defined as an imbalance between the release of vasoprotective vasorelaxant substances, such as nitric oxide (NO), prostacyclin (PGI2), endothelium-derived hyperpolarizing factors (EDHF), and pathological vasoconstricting substances, such as endothelin-1 (ET-1), superoxide, hydrogen peroxide, and thromboxanes.[7] While in large epicardial coronary arteries vasorelaxation is primarily mediated by NO, in small vessels the effect of EDHF is much more pronounced.[8]

2.1 Assessment of coronary microvascular function

The diagnosis of CMD is established by functional assessment of the coronary arteries, which can be done by both invasive and non-invasive methods.[1,9] To assess endothelium-independent microvascular function, the coronary flow reserve (CFR) can be measured, which is defined by the rate of coronary blood flow at hyperaemia compared with baseline. The cut-off for an abnormal CFR is ≤2.5 or 2.0, depending on the technique that is being used.[1] Another parameter that demonstrates endothelium-dependent microvascular function is the microvascular resistance, reported as the index of microvascular resistance (IMR) or the hyperaemic microvascular resistance (hMR). Microvascular resistance is measured during a hyperaemic state with either intracoronary thermodilution (IMR) or Doppler techniques (hMR) and reflect abnormalities in the function and/or structure of the coronary microvasculature. The endothelium-dependent microvascular function can be tested with acetylcholine. In healthy endothelium, acetylcholine results in a net vasodilation because its stimulation of NO and other vasodilators exceeds its direct vasoconstrictor effects on the VSMCs. In CMD, when endothelial function and/or VSMCs function are damaged, NO resources are depleted, and the vasoconstrictor response becomes unopposed.[10]

3. Diabetes mellitus

Patients with diabetes have a three times higher risk of mortality compared with patients without diabetes.[11,12] Microvascular and macrovascular complications are important determinants of morbidity and mortality in DM. Macrovascular complications, including IHD, occur about twice as often in patients with diabetes compared to those without, independent from other risk factors.[13] Microvascular complications, including CMD, are often present before the onset of macrovascular complications. Patients with Type 1 or Type 2 diabetes have a high

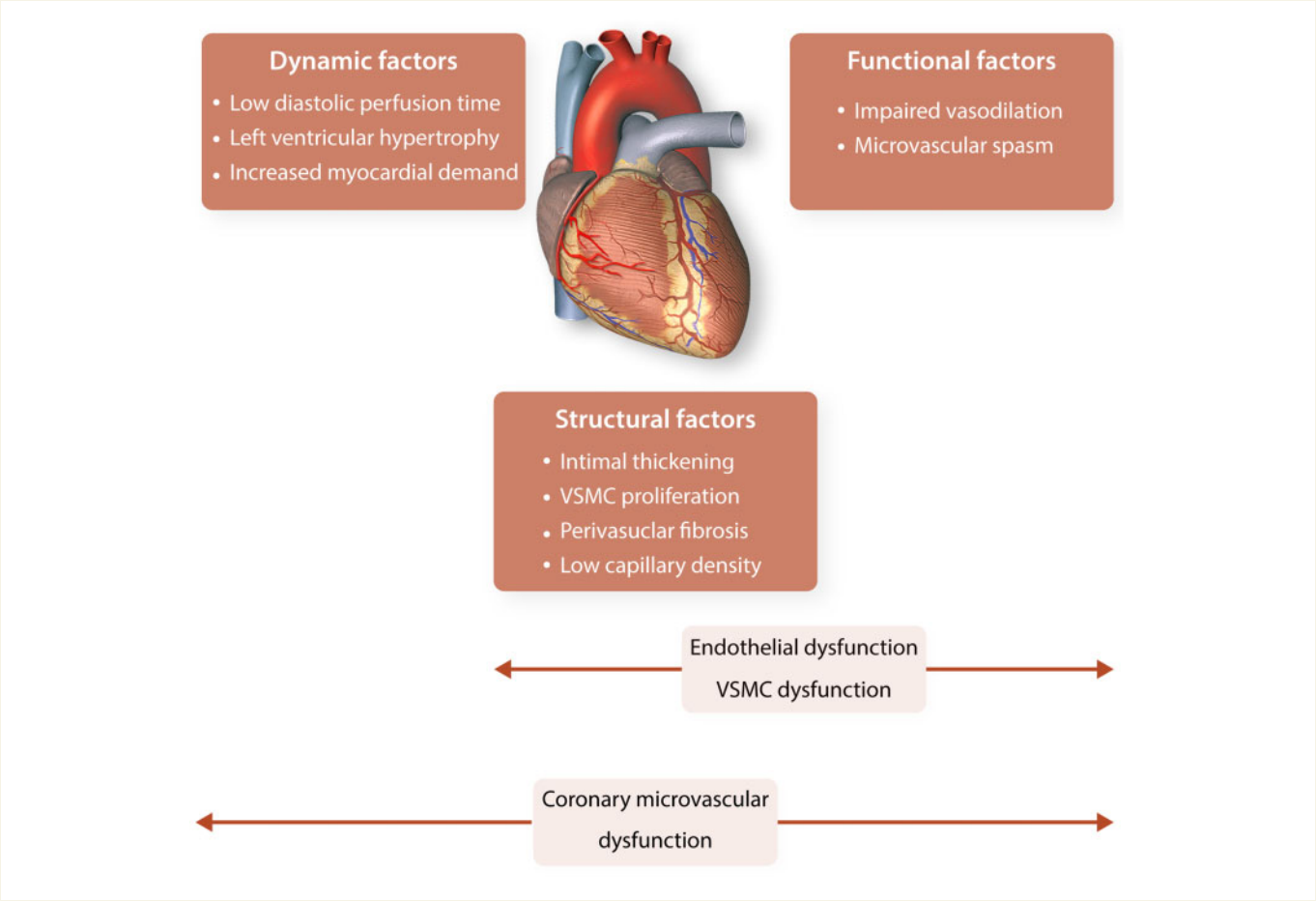

Figure 1 Different factors involved in coronary microvascular dysfunction. Dynamic, structural factors, and functional factors contribute to the occurrence of coronary microvascular dysfunction the presence of other conditions. Endothelial dysfunction and vascular smooth muscle cell dysfunction are caused by (often a combination of) structural and/or functional factors. VSMC, vascular smooth muscle cell.

prevalence of CMD,[14–16] which is a strong predictor of adverse cardiovascular outcome even before macrovascular complications are evident.[15,17] Diabetic patients with a reduced CFR show mortality rates as least as high as those of non-diabetic patients with known obstructive CAD.[18]

3.1 Hyperglycaemia and insulin resistance

Hyperglycaemia and insulin resistance are important factors in the development of CMD in DM.[19] They induce an imbalance between the bioavailability of vasoprotective NO and the accumulation of reactive oxygen species (ROS), as illustrated in *Figure 2*.[19,20]

Hyperglycaemia induces several events—including the activation of protein kinase C (PKC)[21]—that lead to the generation of ROS (e.g. superoxide anion) and oxidative stress.[22] ROS leads to uncoupling of the endothelial NO synthase (eNOS) and to the production of superoxide anion via increased lipid peroxidation products. Superoxide anion reacts with NO to form peroxynitrite, which not only reduces the bioavailability of NO but also reduces the NO production and decreases the responsiveness of tissue to NO.[23,24] Superoxide anion also increases the production of ROS via advanced glycation end products (AGEs) and activation of the receptor for AGE on vascular cells.[21] These processes likely recruit xanthine oxidase, leading to a further increase in ROS levels and augmenting oxidative stress.[25]

Insulin resistance contributes to this detrimental process by decreasing the activity of eNOS and reducing the production of NO, resulting in less available vasoprotective NO.[22] The mainly NO-driven endothelium-dependent vasoreactivity is related to insulin resistance and has been shown to improve when insulin resistance improves using metformin treatment.[26] The hyperinsulinaemia in DM is also associated with elevated levels of free fatty acids[27,28] that contribute to oxidative stress and a proinflammatory state by activating PKC, increasing the production of ROS, and exacerbating dyslipidaemia.[29,30]

3.2 Proinflammatory state

Many of the aforementioned processes contribute to the activation of the endothelium to a proinflammatory state, resulting in the enhanced endothelial expression of adhesion molecules such as intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and E-selectin, the release of proinflammatory cytokines, the migration and proliferation of VSMCs, and an increased synthesis of endothelin. Progressive arterial stiffness and a higher prothrombotic state further contribute to the development of CMD and macrovascular complications in patients with DM.[22,31–33] These proinflammatory cytokines are not only implicated in the pathogenesis of DM but may also contribute to the development of CMD and IHD.[33]

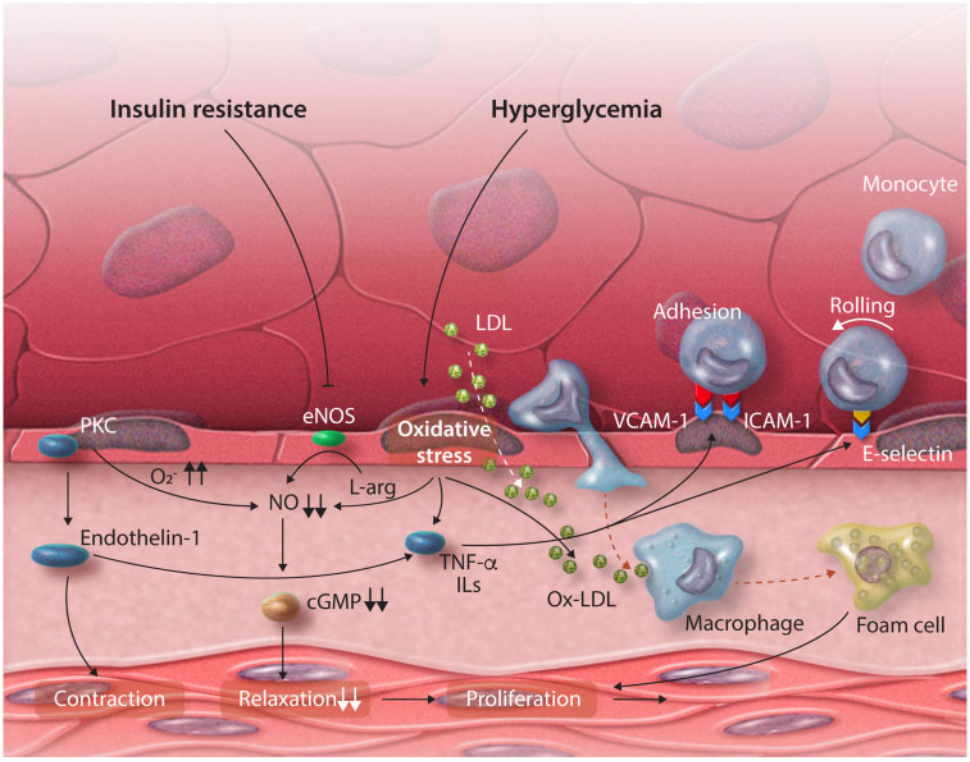

Figure 2 Schematic overview of the pathophysiological mechanisms of coronary microvascular dysfunction in diabetes. Both hyperglycaemia and insulin resistance contribute to oxidative stress, the release of proinflammatory cytokines and the decrease of the nitric oxide availability. cGMP, cyclic guanosine monophosphate; eNOS, endothelial nitric oxide synthase; ICAM-1, intercellular adhesion molecule-1; ILs, interleukins; LDL, low-density lipoprotein; NO, nitric oxide; Ox-LDL, oxidized LDL; PKC, protein kinase C; TNF-α, tumour necrosis factor alpha; VCAM-1, vascular cell adhesion molecule-1.

The cycle of inflammation and oxidative stress, does not only affect cardiac cells but also induces cell damage in pancreatic beta-cells, further enhancing DM. Treatment should therefore be aimed at managing all factors that contribute to this vicious cycle. Glycaemic control is key in diabetics and even little variations in glycaemic state are important in maintaining a healthy vascular state.[34,35] Long-term aggressive management of co-existing traditional cardiovascular risk factors reduces the risk of cardiovascular events in patients with Type 2 DM by about 50% and should be implemented in the treatment of patients in an early stage.[36–38] Although we await studies to confirm this, we believe that patients with both diabetes and a reduced CFR could benefit even more from aggressive preventive and treatment strategies.

4. Obesity and CMD

Obesity, defined as body mass index (BMI) 30 kg/m^2 or higher, is one of the ongoing epidemics in industrialized countries. Some obese individuals are at an increased risk of developing cardiovascular events.[39] The mechanisms responsible for increased cardiovascular risk in obesity, however, are complex and may vary in different individuals. Increased oxidative stress, low-grade systemic inflammation, and increased sympathetic nervous system activity have been postulated as risk factors, as they can lead to CMD and reduced CFR[40], which is, in turn, associated with impaired clinical outcomes including increased mortality.[41,42] Positron emission tomography (PET) flow studies[43] carried out in 'metabolically healthy' obese individuals (i.e. obesity without systemic hypertension, dyslipidaemia or diabetes) have shown CFR abnormalities to be present in these persons. Recently, Bajaj *et al.*[44] assessed the relationship between BMI and CMD, and their possible link with adverse cardiovascular events in patients with and without obesity. They found that in obese patients, CFR decreased linearly with increasing BMI and was independently associated with cardiovascular events. In obese patients, individuals with impaired CFR showed a higher adjusted rate of cardiovascular events (5.7% vs. 2.6%; $P = 0.002$).[44] CMD was independently associated with elevated BMI and adverse clinical outcomes. Moreover, CFR was a better marker of risk than both BMI and conventional cardiovascular risk factors. This was a retrospective study involving 827 subjects undergoing rest and stress myocardial perfusion testing with ^{13}N-ammonia or ^{82}rubidium PET. Clinical endpoints defined as a composite of death or non-fatal myocardial infarction or heart failure were assessed during follow-up (median follow-up 5.6 years). In the Bajaj study,[44] BMI and CFR both were good prognostic markers, but only CFR was independently associated with events. Of interest, only obese patients with reduced CFR—particularly those with a very high BMI (30–39 kg/m^2)—had increased cardiovascular risk, i.e. ≥2.5-fold increased rate of events. An impairment of the vasodilatory capacity of the coronary circulation has been shown to precede the development of obstructive CAD.[45]

In obese patients, there is growing evidence of the association among increased BMI, metabolic abnormalities, and systemic inflammation, probably as a result of the actions of adipocytokines such as leptin, adiponectin, interleukin-6 (IL-6), and tumour necrosis factor alpha (TNF-α) on

microvascular function[40] suggesting a pathogenic link between obesity and CMD. Current and previous research[43] suggest that an imbalance among obesity-related metabolic abnormalities, endocannabinoids, and adipocytokines may be key determinants of CMD in obesity.[43] The notion that a reduced CFR due to CMD rather than just 'obesity', is associated with impaired outcomes in obese patients has pathophysiological and therapeutic importance. Cardiovascular risk may vary in different obese individuals and not all may benefit from the same preventative or therapeutic measures. Individuals with severe CMD may benefit from treatments addressing the many pathogenic mechanisms that lead to a reduced CFR in this patient group. However, future research on this subject is much awaited.

5. Hypertensive pregnancy disorders

HPD complicate 5–15% of pregnancies. The most severe form of HPD is pre-eclampsia, occurring in 3–5% of all pregnancies.[46,47] The International Society for the Study of Hypertension (ISSHP) defines pre-eclampsia as new-onset hypertension after 20 weeks gestation in combination with either proteinuria (≥300 mg/day) or other maternal dysfunctions, such as renal insufficiency, liver involvement, neurological or haematological complications, or uteroplacental dysfunction.[48] Unlike previous beliefs that HPD are self-limiting conditions that resolve after delivery of the placenta, we now know that women with HPD have an up to eight-fold increased risk of cardiovascular disease (CVD) later in life.[47,49] HPD should be regarded as a window into future maternal cardiovascular health; evidence points towards a partially shared pathophysiology in HPD and CVD.[50]

A combination of maternal and placental factors is considered to be responsible for the development of HPD, in which an increased inflammatory response and maternal (systemic) endothelial dysfunction are key features.[51] In many women with HPD, there is a pre-existing (genetically) increased risk for CVD. Signs of an abnormal systemic endothelial function are present even before the onset of pre-eclampsia, possibly related to an already enhanced inflammatory state.[52] The placenta itself is also important in the pathogenesis of HPD. An abnormal placentation in early pregnancy (e.g. abnormal invasion of trophoblasts and inadequate maternal spiral artery remodelling) causes placental malperfusion and hypoxia.[53,54] This results in oxidative stress, a generalized hyperinflammatory state and an exaggerated endothelial activation.[55] During pre-eclampsia, several markers of inflammation, such as TNF-α, IL-6, IL-17, and vasoconstrictor ET-1, are substantially increased in the maternal circulation and the placenta.[56] The hyperinflammatory state and the systemic endothelial dysfunction that occur in HPD, seem to persist postpartum, which may underlie the development of CVD later in life. Months to years after delivery, affected women remain to have increased plasma concentrations of inflammatory markers compared with women who had a normal pregnancy, i.e. higher baseline levels of C-reactive protein (CRP), IL-6 and fibrinogen,[57] and alterations in TNF-α, IL-6, leptin, adiponectin, homocysteine, soluble E-selectin, and pregnancy-associated plasma protein-A.[58–62] An increase in the CRP response to vaccination and a consistent pattern of increased acute-phase responses to vaccination for all inflammatory markers were also found among women after pre-eclampsia compared with controls, indicating that vascular responses are altered afterwards.[63]

5.1 CMD and IHD after pre-eclampsia

These altered vascular responses are also observed in the coronary circulation: an impaired CFR and other signs of CMD have been shown in women up to several years after pre-eclampsia compared with women who had a healthy pregnancy and delivery (2.39 ± 0.48 vs. 2.90 ± 0.49; $P < 0.001$).[64,65] Although prospective data are lacking, many of these women mention MVA in their fifth and sixth decade. An important trigger for MVA in these patients is premature hypertension. Premature signs of subclinical CAD have been demonstrated by carotid intima-media thickness measurements and coronary artery calcium scores in middle-aged women after pre-eclampsia.[64,66–68] This reflects their two-fold higher risk to develop IHD.[69] At an older age, these women may develop heart failure with preserved ejection fraction, in relation to their long-standing hypertension and enhanced inflammatory state. More prospective data are needed to better identify the life-course of women after pre-eclampsia and to determine most optimal strategies for prevention. The primary prevention guidelines are currently used for the follow-up of these high-risk women, but secondary prevention guidelines may be more appropriate.[70] In this perspective, it would be interesting to study the benefit of preventive strategies in women with early signs of cardiovascular abnormalities, such as the presence of CMD.

6. Chronic inflammatory and autoimmune rheumatic disorders

In recent years, it has become apparent that cardiovascular risk is particularly increased in patients with inflammatory disorders.[71,72] In rheumatoid arthritis (RA), a meta-analysis of total of 41 490 cases showed that cardiovascular risk was increased by 48%, when compared with individuals without RA [pooled relative risk 1.48 (95% confidence interval 1.36–1.62)].[73] Similar observations of increased risk have been made for other autoimmune or inflammatory diseases including ankylosing spondylitis (AS),[74] psoriatic arthritis (PA),[75] as well as systemic lupus erythematosus (SLE).[76] Experimental studies, which allow to better control study conditions show that this increase is in part linked to common cardiovascular risk factors between these comorbidities,[77] but to the large extent depend on the role of inflammation as a risk factor of CVD.[78] Similarly, endothelial dysfunction is a key mechanism for both obstructive and non-obstructive forms of CAD,[79] linked to both classic cardiovascular risk factors and to inflammation.[80] In large vessels, endothelial dysfunction and stiffening has been widely described in a wide spectrum of inflammatory conditions. The examples include psoriasis,[81] periodontitis,[82,83] or inflammatory bowel disease.[84] Microvascular dysfunction has also been widely described in patients with inflammatory joint diseases.[85,86] A recent meta-analysis in 709 patients with rheumatic disease and 650 controls,[87] showed a significantly reduced CFR in patients with various forms of arthritis. Patients with autoimmune disease such as SLE had significantly lower CFR than subjects with mixed autoinflammatory/autoimmune disorders, such as RA or PA.[87] Indeed, recent 5-year follow-up study in SLE patients showed significant non-obstructive impairment of myocardial perfusion in more than half of the patients with SLE.[88] However, coronary as well as peripheral microvascular dysfunction have been observed already in early RA even after 6 months since initial diagnosis.[89] Several studies have also shown systemic microvascular dysfunction as measured in peripheral vascular beds in patients with RA and AS.[72,90] Interesting insight into the CMD can be gained from the analysis of skin microvasculature, which has been shown to offer a useful

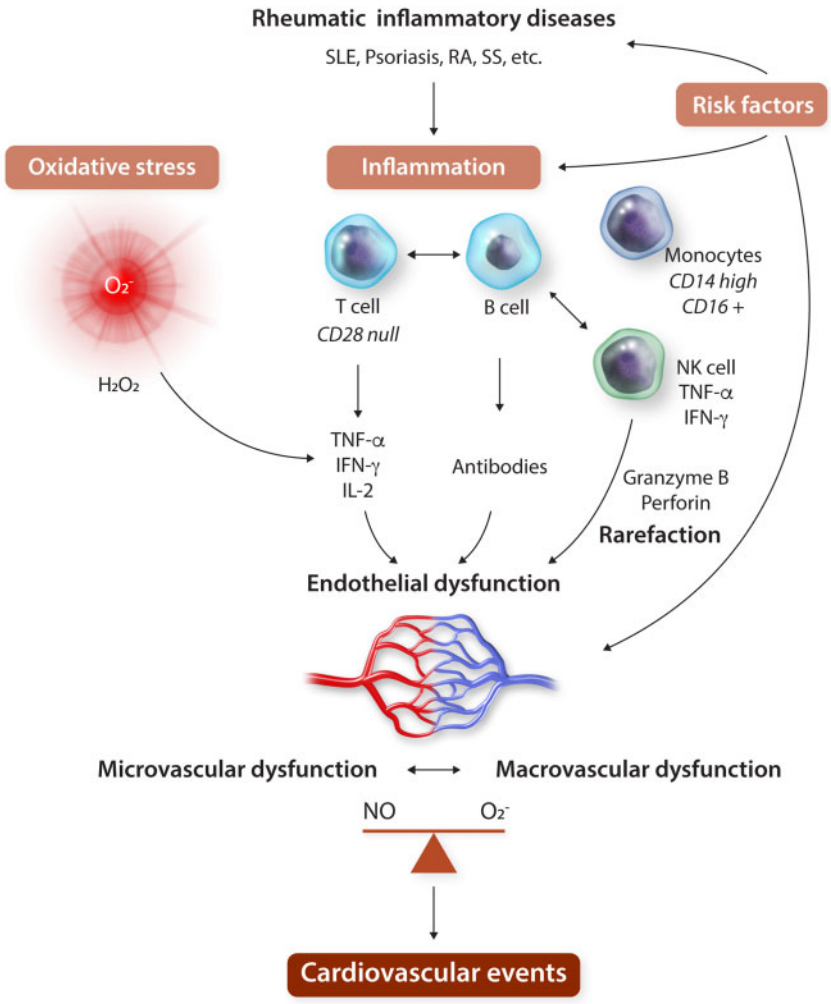

Figure 3 Schematic overview of the mechanisms involved in the systemic endothelial dysfunction that is present in patients with rheumatic inflammatory diseases, in relation to the occurrence of cardiovascular events. IFN, interferon; IL-2, interleukin-2; PA, psoriatic arthritis; RA, rheumatic arthritis; RFs, risk factors; SLE, systemic lupus erythematosus; SS, systemic sclerosis; TNF, tumour necrosis factor.

model to study arteriole function and capillary morphology.[91] Findings from these studies are in line with earlier invasive observations that NO-mediated, acetylcholine-induced vasorelaxation in microvessels is impaired in AS and may improve with anti-TNF-α therapy.[86,90] In similarity to large vessel endothelial dysfunction, microvascular dysfunction has been identified in a number of inflammatory conditions, such as severe chronic periodontitis,[92] or inflammatory bowel disease,[93] where impairment correlates with CRP. Thus, inflammation may provide a mechanistic link between these comorbidities and cardiovascular events.

6.1 Mechanisms contributing to CMD in rheumatoid disorders

Clinical meta-analyses of CFR in rheumatic disease do not seem to provide sufficient hints regarding the mechanisms that cause CMD. Across over 20 studies in several rheumatic diseases, reductions of CFR were not linked with either inflammatory burden, lipids, BMI, age, or even blood pressure.[87] It is particularly surprising that some large studies, such as a longitudinal Dudley Rheumatoid Arthritis Comorbidity Cohort (DRACCO) study, did not show any association between cumulative inflammatory burden as measured with CRP or erythrocyte sedimentation rate (ESR), and endothelial function after 6 years follow-up.[94] However, the observational nature of this study and the use of solely CRP and ESR to measure inflammation leave the main question of the relationship between inflammation and CMD open. In fact, other studies have shown that clinical inflammatory burden in patients with AS is associated with microvascular flow impairment.[72] Notably, some interventional evidence shows that anti-inflammatory biological therapies such as anti-TNF treatments lead to improvement of coronary and peripheral microvascular dysfunction,[90] although results are often conflicting and not emerging from randomized or placebo-controlled studies.[72]

Most preclinical and observational studies point to an important mechanistic importance of systemic endothelial dysfunction in rheumatic disease, which seems to coincide with or precede both macro- and microvascular disease/dysfunction.[95] A schematic overview is provided in *Figure 3*. Systemic endothelial dysfunction is linked with increased

oxidative stress, possibly up-regulation of NADPH oxidases (Nox) as well as vascular mitochondrial dysfunction.[7] Increased ROS production is part of the pathogenesis of arthritis as it is induced in endothelial and VSMCs by a number of inflammatory mediators including IL-17, interferon-γ (IFN-γ), and TNF-α.[7] In fact, these proinflammatory cytokines are known to induce and activate Nox enzymes.[80,96–98] Oxidative stress is reported both locally and systemically in mouse models of RA.[99] Interestingly, there is a two way interaction between vascular renin–angiotensin aldosterone system (RAAS) activation, which is closely linked to oxidative stress, and disease activity in RA or SLE. Angiotensin receptor blockers inhibit Nox expression and activation and have been shown to improve endothelial function in animal models of arthritis.[100] Together, this evidence suggests that oxidative stress may be intrinsically involved in establishing and potentiating RA-associated vascular damage both locally and systemically.

Mechanistically, the L-arginine analogue asymmetric dimethylarginine (ADMA) has been suggested to play a role in with CMD in RA.[72] ADMA reduces NO production and promotes endothelial dysfunction by a competitive inhibition of NOS. However, in further observational studies, neither coronary nor skin microvascular endothelial function correlated with ADMA.[101] This might indicate that microvascular dysfunction in rheumatic diseases may be less dependent on this mechanism.

A number of immune cells, specifically those involved in the pathogenesis of arthritis and rheumatic disorders, have been implicated in the pathogenesis of endothelial dysfunction and CMD in rheumatic disorders as well.[102] Cell type indicated by clinical studies include T-cells, natural killer (NK) cells and monocytes. Notably, immune deficient mice lacking T-cells, B-cells, and NK-cells or mice lacking only T- and B-cells present smaller diameters of microvasculature (third-order cremaster arterioles). Vasoconstriction of these vessels is particularly promoted by NK-cells[103] as well as potentially dysregulated CD28null (CD4+ and CD8+) that produce proinflammatory cytokines known to induce oxidative stress and endothelial dysfunction (IFN-γ, TNF-α, and IL-2) and may also cause arteriolar rarefaction.[104,105] These cells are also a hallmark of other chronic inflammatory conditions such as periodontitis, and they decrease upon successful intensive therapy of periodontitis.[83] Lymphocyte involvement in the vascular pathology in patients with inflammatory disease is closely linked to oxidative stress. For example, Nox2 is expressed by T-cells and antigen presenting cells and mediates their activation and ability to serve homeostatic immune functions.[106,107] We have also identified that in particular proinflammatory monocytes, CD14(high)CD16+ are related to endothelial dysfunction in arthritis patients,[108] while in general CAD population a different subset of monocytes (CD14dimCD16+) were primarily correlated.[109] While a number of cell types may be involved, final effectors of this response appear to be linked to overexpressed cytokines. An elegant study by Ahmed *et al.*[110] has shown that in dysfunctional vasculature of patients with RA, a particular overexpression of IL-18, IL-33, and TNF is observed which may play a role in the inflammatory process and the development of endothelial dysfunction.

6.2 Implications

Understanding the unique mechanisms of CMD in chronic inflammatory and rheumatic diseases may allow for a more specific diagnosis and prevention. In particular understanding the relationship between clinical disease severity, inflammatory burden, and the development of CVD is essential. Understanding the role of individual cell types and cytokines in this process may allow more direct targeting in the future. Statins may represent a simple and unspecific approach to reduce systemic inflammation while at the same time statins target other mechanisms of microvascular dysfunction. Recently, specific trials of immune-targeted therapies in CVD, namely the Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS) trial and the Cardiovascular Inflammation Reduction Trial (CIRT) have tested the utility of IL-1β and methotrexate targeting in the prevention of major cardiovascular events showing that modes of targeting are essential for outcomes, as discussed by us extensively elsewhere.[111] However, while they provide proof-of-concept, lack of focus on CMD was present in either of these trials, which makes it difficult to extrapolate their results. It is clear that we should diagnose and actively search for CMD in patients with rheumatic inflammatory and autoimmune disorders as this population is of particularly high risk.

7. Chronic kidney disease

CKD is a known risk factor for CVD. For a long time, this risk was assumed to be the result of the high prevalence of traditional cardiovascular risk factors. Indeed, hypertension and diabetes are the main causes of CKD. Also, CKD promotes the development of hypertension by activation of the RAAS system, sodium retention and increased concentrations of catecholamines. However, meta-analyses have clearly shown that an impaired kidney function is a cardiovascular risk factor independently of the presence of other traditional cardiovascular risk factors.[112] Patients with an estimated glomerular filtration rate (eGFR) below 15 mL/min/1.73 m^2 still have a three times higher risk of cardiovascular death compared to those with a normal kidney function, even when adjusted for other risk factors.[113] The number of deaths from CVD increases as eGFR rate decreases.[112] Besides cardiovascular death, patients with CKD are also at risk for developing CVD, e.g. diastolic dysfunction, left ventricular hypertrophy (LVH), or IHD, referred to as Type 4 cardiorenal syndrome.[114] CMD is one of the key features in the pathophysiology of this syndrome. CMD, measured as a reduced CFR, is present in many patients with CKD compared with healthy controls.[115,116] And, concordant with what we have discussed in the other sections of this article, the CFR is independently associated with adverse cardiovascular events.[117,118]

7.1 The link between CMD and cardiorenal syndrome

It is assumed that uraemia-specific mechanisms contribute to CMD and CVD in patients with CKD.[119] It has been shown that uraemia promotes microvascular rarefraction.[120] In post-mortem samples, patients with CKD have an almost 50% decrease in capillary density in the heart.[121,122] Moreover, uraemia induces a state of oxidative stress and an increased inflammatory state by several mechanisms,[123] an enhanced activity of NAD(P)H oxidase,[124] a reduced bioavailability of NO caused by an increase in the NO-synthase inhibitor ADMA,[122] and increased levels of inflammatory markers (i.e. CRP, TNF-α, IL-1β and IL-6).[125] As we have discussed before, oxidative stress and inflammation link to CMD.

The most common phenotype of the Type 4 cardiorenal syndrome is LVH: nearly 75% of adults with end-stage renal disease have signs of LVH[126] and the severity of LVH is an independent predictor for mortality.[127] Both the abovementioned uraemia-specific mechanisms as well as other CKD-specific mechanisms contribute to this cardiomyopathy, including hypertension, increased vascular stiffness, increased levels of steroid hormones, and activation of the RAAS system.[128,129]

It is evident that CKD and CVD enhance each other. Future research should focus on unravelling the causality between uraemia-specific mechanisms, CMD and the development of CVD in these patients. These insights could aid preventive strategies and treatment regimens.

8. Hypertrophic cardiomyopathy

HCM is the most common genetic heart disease, with a prevalence of 1:500 in the general population and is defined by the presence of primary LVH that is not explained by abnormal loading conditions.[130,131] Myocardial ischaemia often occurs in patients with HCM, even in the absence of clinical symptoms.[132–135] The substrate for myocardial ischaemia are perfusion defects, as represented by a reduced CFR in patients with HCM.[136] These perfusion defects are often subendocardial and are most pronounced in the most hypertrophied (septal) segments.[137,138] Perfusion abnormalities are associated with the presence of myocardial fibrosis,[138] and fibrosis contributes to life-threatening electrical instability in HCM.[133,135,139]

Even though the assessment of CFR in HCM is not yet incorporated in HCM management guidelines or risk algorithms, the presence of CMD can identify patients at risk and those with no signs of CMD seem to have a relative good prognosis.[140] The degree of CMD is a strong and independent predictor of clinical deterioration and death.[135,141] CMD also predicts long-term adverse left ventricular (LV) remodelling and systolic dysfunction, even in patients with no or mild symptoms and normal LV function,[140,141] making it a potential target for the prevention of disease progression in HCM.

8.1 Different mechanisms contribute to CMD in HCM

CMD is more than just a supply/demand mismatch caused by the overall increase in metabolic demand of the increased myocardial mass in patients with HCM. Both structural and functional alterations are important factors in CMD and subsequent myocardial ischaemia. Already decades ago, histopathological studies showed that HCM patients have markedly abnormal coronary microvasculature structure: the luminal areas of the arterioles are severely reduced due to intimal hyperplasia or medial hypertrophy,[133,142,143] and HCM patients have a lower number of capillaries and lower capillary density compared with normal controls.[144] These changes are observed in both hypertrophic obstructive cardiomyopathy and end-stage HCM, but myocardial fibrosis is more severe in end-stage HCM.[145] The more functional and dynamic factors associated with CMD in HCM are perfusion abnormalities that result from a deranged coronary blood flow throughout both systole and diastole.[146] In the hypertrophied hearts, compression of the intramyocardial arterioles during ventricular systole results in less coronary flow, as shown by wave intensity analysis.[146] This compression causes elevated pressures in the microcirculation that can stop or even reverse flow in the epicardial coronary arteries, a phenomenon that worsens during hyperaemia. In patients with transient LV outflow tract obstruction, blood flow is even further decreased during systole. In addition to these derangements during systole, there is a decrease in coronary flow during diastole as well, related to an impaired ventricular relaxation and increase in passive stiffness.

8.2 Clinical implications

It is unlikely that treatment will reverse the structural changes in the microvasculature of HCM once they are present. However, the presumably preceding dynamic changes, marked by a decreased CFR, could be influenced by medical interventions. Septal ablation has been shown to improve CFR and blood flow dynamics.[147] The use of beta-blockers and calcium channel antagonists are interesting in this regard as well, for they theoretically increase diastole and decrease the contractile forces that reduce CFR. Whether these interventions decrease or prevent subendocardial ischaemia and subsequent fibrosis needs to be studied in more detail in prospective trials.

9. Aortic valve stenosis

Another condition that is associated with LVH is AoS, in which the LVH develops in response to pressure overload. Men and women with similar degrees of AoS have different LV adaptations to this pressure overload. Women more frequently have a greater degree of LVH, higher relative wall thickness, smaller end-systolic and end-diastolic chamber size.[148] The development of LVH is accompanied by the development of CMD in AoS.[149,150] As we have learned in the previous paragraph of this manuscript, LVH is associated with a functionally deranged coronary blood flow, while oxygen demands increase,[151] causing cardiac ischaemia. Related to the pressure drop across the aortic valve, there is less systolic acceleration of coronary blood flow in patients with AoS compared to healthy controls.[152] In addition to this, coronary arteries are compressed to a larger extent in the hypertrophied and pressure-overloaded left ventricle during isovolumetric contraction when the aortic valve is still closed, causing a decrease of coronary blood flow in this period of the heart cycle.[153] A reduced diastolic perfusion time during exercise and a high diastolic wall stress add to this blood flow maldistribution during exercise or hyperaemia, resulting in a decreased CFR and subendocardial myocardial ischaemia during stress[149] related more to the severity of AS (valve effective orifice area), haemodynamic load, and reduced diastolic perfusion time rather than to the increase in LV mass.

Studies have even shown that the reduced CFR in AoS is more related to the severity of AoS (i.e. the valve effective orifice area),[154] haemodynamic load, and reduced diastolic perfusion time than it is to the increase in LV mass.[149] In line with this observation is the direct improvement of the CFR after successfully treatment of AS is with a transcatheter aortic valve replacement (TAVR): immediately after TAVR baseline haemodynamics remain unchanged, whereas hyperaemic parameters are improved, if there is no important aortic regurgitation.[155] Unlike in HCM, the coronary microvasculature of patients with severe AoS show no signs of intramural medial hypertrophy, making it unlikely that structural changes of the microvasculature contribute significantly to CMD in patients with AoS.[156] The presence of CMD is associated with angina but not all patients with AoS and angina show signs of CMD.[157,158] CMD could however play a significant pathophysiological role in the natural history of AoS contributing to the development of cardiac fibrosis and LV dysfunction. CFR was found to be an independent predictor for future cardiovascular events in AoS patients in one small study.[159]

In the treatment of patients with AoS, it has been shown beneficial to focus on the mechanisms involved in the dynamic alterations in coronary flow that are associated with CMD and myocardial ischaemia, such as the short diastolic time. A propensity-matched *post hoc* analysis showed that betablocker use reduces all-cause mortality (hazard ratio 0.5, 95% confidence interval 0.3–0.7; $P < 0.001$), cardiovascular death (hazard ratio 0.4, 95% confidence interval 0.2–0.7; $P < 0.001$), and sudden cardiac death (hazard ratio 0.2, 95% confidence interval 0.1–0.6; $P = 0.004$) in 1873 asymptomatic patients with mild to moderate AoS and preserved

LV ejection fraction.[160] The ultimate treatment of severe symptomatic AS is aortic valve replacement. It would be interesting to study if CMD could aid in choosing the optimal timing of this intervention before extensive myocardial fibrosis is present.

10. Summary and future perspectives

CMD can occur in the setting of a wide variety of cardiac and systemic clinical conditions, and often results from changes in microvascular structure, microvascular function, and/or a maldistribution of coronary blood flow. Despite the various mechanisms involved in the presence of CMD in the discussed clinical conditions, CMD is consistently associated with myocardial ischaemia and portrays an increased risk for cardiovascular events. CMD is often detectable very early in the course of the primary disease, before clinical symptoms or signs of myocardial ischaemia are present. These observations support the potential use of CMD in strategies for risk stratification, which should be explored further. Novel agents that target-specific pathways that lead to endothelial damage and a proinflammatory state are an active area of research at present and could provide novel insights regarding the management of both the primary disorders and the associated CMD.

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