American Heart Journal Plus: Cardiology Research and Practice 22 (2022) 100215

Contents lists available at ScienceDirect

American Heart Journal Plus: Cardiology Research and Practice

journal homepage: www.sciencedirect.com/journal/american-heart-journal-plus-cardiology-research-and-practice

Research paper

Critical role of the coronary microvasculature in heart disease: From pathologic driving force to "innocent" bystander

Roshni O. Prakash [a,1], Teja S. Chakrala [a,1], Daniel S. Feuer [a], Carlos A. Valdes [a], Carl J. Pepine [a,b], Ellen C. Keeley [a,b,*]

[a] Department of Medicine, University of Florida, Gainesville, FL, United States of America
[b] Division of Cardiovascular Medicine, University of Florida, Gainesville, FL, United States of America

ARTICLE INFO

Keywords:
Coronary microvascular dysfunction
ANOCA
INOCA
MINOCA

ABSTRACT

The coronary microvasculature is responsible for providing oxygen and nutrients to myocardial tissue. A healthy microvasculature with an intact and properly functioning endothelium accomplishes this by seemless changes in vascular tone to match supply and demand. Perturbations in the normal physiology of the microvasculature, including endothelial and/or vascular smooth muscle dysfunction, result in impaired function (vasoconstriction, antithrombotic, etc.) and structural (hypertrophic, fibrotic) abnormalities that lead to microvascular ischemia and potential organ damage. While coronary microvascular dysfunction (CMD) is the primary pathologic driving force in ischemia with non-obstructive coronary artery disease (INOCA), angina with no obstructive coronary arteries (ANOCA), and myocardial infarction with non-obstructed coronary arteries (MINOCA), it may be a bystander in many cardiac disorders which later become pathologically associated with signs and/or symptoms of myocardial ischemia. Importantly, regardless of the primary or secondary basis of CMD in the heart, it is associated with important increases in morbidity and mortality. In this review we discuss salient features pertaining to known pathophysiologic mechanisms driving CMD, the spectrum of heart diseases where it places a critical role, invasive and non-invasive diagnostic testing, management strategies, and the gaps in knowledge where future research efforts are needed.

1. Coronary microvasculature

The coronary vasculature, comprised of the epicardial vessels and the coronary microvasculature, is tasked with providing oxygen and nutrients to and removing waste from the myocardium. From proximal to distal, they decrease in size and carry out distinct functions. Epicardial arteries (also known as conduit arteries) are >500 μm in size and their role is to transport blood with minimal resistance. The coronary microvasculature represents all vessels distal to the conductive arteries, including pre-arterioles and arterioles, capillaries, membrane, venules, and pericytes [1]. The coronary microvasculature is the essential determinant of myocardial perfusion, by matching myocardial blood and nutrient supply to cardiac work [2]. Pre-arterioles and arterioles are key regulators of blood flow. Pre-arterioles (~100–500 μm in size) are effective in maintaining a narrow range of pressure at the origin of arterioles despite changes in coronary perfusion. Arterioles (<100 μm in size) function to match blood supply with local oxygen demand via a dilatation response to local metabolites [1]. Capillaries, the most distal and smallest component of the microvasculature (<10 μm), are the primary site of gas and nutrient exchange [3]. Other important components, but less well studied, include pericytes, the membrane, and venules [4].

Acute changes in coronary blood flow mainly occur in response to neurogenic mechanisms as metabolic stimuli are responsible for slower changes and are regulated by microvascular tone through myogenic and flow-mediated responses [5]. Chronic adjustments involve structural remodeling of the coronary microvasculature via changes in the vascular tone regulated by endothelial and metabolic factors along with mechanical forces such as shear stress acting on the endothelium with resulting effects on underlying vascular smooth muscle cells [6]. Perturbations in these mechanisms lead to the pathologic state of coronary microvascular dysfunction.

* Corresponding author at: University of Florida, Division of Cardiovascular Medicine, P.O. Box 100288, 1329 SW 16th Street, Gainesville, FL 32610-0288, United States of America.
E-mail address: Ellen.Keeley@medicine.ufl.edu (E.C. Keeley).
[1] These authors contributed equally.

https://doi.org/10.1016/j.ahjo.2022.100215
Received 29 August 2022; Accepted 30 September 2022
Available online 1 October 2022

2. Coronary microvascular dysfunction

Coronary microvasculature dysfunction (CMD) is a result of functional and structural abnormalities of the pre-arterioles, arterioles, and capillaries, culminating in myocardial tissue ischemia, necrosis, and subsequent dysfunction. Clinically, CMD may present as angina-like chest pain with no flow-limiting epicardial coronary artery stenosis on coronary angiography [7]. It is an important clinical entity to recognize since patients with chest pain and no flow-limiting epicardial coronary artery disease may be misdiagnosed as having non-cardiac chest pain. Risk factors for CMD include traditional cardiovascular risk factors such as hypertension, diabetes mellitus, hyperlipidemia, and smoking. Additional risk factors for CMD include female sex, younger age, and chronic inflammatory conditions such as systemic lupus erythematosus and rheumatoid arthritis [8–11]. Female sex is a particularly important risk factor; women of peri- or post-menopausal age typically present with greater number and severity of CMD risk factors than men [8]. In fact, nearly half of women who present with chest pain and no obstructive coronary arteries have CMD [12].

Chronic inflammatory states are also associated with CMD. Patients with chronic inflammatory and autoimmune disorders have CMD as assessed by reduced coronary flow reserve (CFR) in the presence of non-obstructive coronary artery disease (CAD) [13–15]. Elevated high-sensitivity C-reactive protein levels have been documented in subjects with CMD compared to control subjects, suggesting a chronic inflammatory condition [13,16].

The pathophysiology of CMD encompasses both functional and structural abnormalities including endothelial dysfunction, impaired autoregulation, vasospasm, and microthrombosis. Under normal conditions the coronary endothelium produces vasoactive agents, such as nitric oxide and prostacyclin, to maintain adequate perfusion. An imbalance between vasodilators and vasoconstrictors (favoring vasoconstriction) impairs coronary blood flow [17]. This phenomenon is of paramount importance in the heart because at rest there is a near maximal oxygen extraction such that any increased oxygen demand must be met with proportionally increased coronary blood flow. In CMD, the ability to increase coronary blood flow is attenuated, resulting in myocardial ischemia at times of increased myocardial oxygen demand [18]. Microvascular remodeling consisting of luminal narrowing of the intracardiac arterioles and capillaries, perivascular fibrosis, and destruction of the capillary bed (capillary rarefaction) are pathologic processes that lead to increased arteriolar resistance and decreased tissue perfusion in CMD [3]. Microvascular remodeling resulting in CMD can also occur in patients with flow-limiting epicardial coronary artery disease, providing an explanation as to why anginal symptoms may persist after percutaneous or surgical revascularization of epicardial artery disease [19]. Coronary vasospasm is another significant contributor to CMD in patients with microvascular angina and is associated with endothelial dysfunction. In one study, nearly half of patients with stable angina had normal or near-normal coronary angiograms, but vasoreactivity testing with acetylcholine induced epicardial and/or microvascular coronary spasm in nearly two thirds of them [20]. Lastly, microthrombosis is another pathologic process that is operational in CMD. Elevated serum thrombomodulin (an anti-coagulant) levels have been documented in patients with CMD which is considered a compensatory response that is associated with decreased adverse cardiac events [21,22].

3. Spectrum of coronary microvascular dysfunction

This pathologic entity is now referred to as symptoms and/or signs of ischemia with non-obstructive coronary artery disease (INOCA) and angina with no obstructive coronary arteries (ANOCA). Furthermore, it is well accepted that it is not a benign condition and rather is associated with significant morbidity and mortality [23]. It is important to note that while INOCA and ANOCA is predominantly diagnosed in women, it also affects men [23,24]. Data from the Women's Ischemia Syndrome Evaluation (WISE) study suggest that patients with persistent chest pain and no obstructive epicardial coronary artery disease have worse clinical outcomes compared to those without persistent pain including a near 2-fold increase in the risk of myocardial infarction and stroke [25].

Myocardial infarction with non-obstructed coronary arteries (MINOCA) is also common, occurring in 5–10 % of all myocardial infarctions, particularly in younger women with fewer traditional risk factors presenting with non-ST elevation myocardial infarction [26]. The diagnosis of MINOCA is made clinically following coronary angiography that shows no coronary artery stenosis $\geq$50 % in a potential infarct-related artery [27]. In the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial the prevalence of MINOCA was ~9 % [28], and one-year non-cardiac death was significantly higher in those with MINOCA compared to those with obstructive disease [28]. While there are some data to suggest that treatment with the standard medications usually prescribed post-myocardial infarction in cases of obstructive disease may be beneficial [29], randomized controlled trial data are lacking. Moreover, due to the heterogenous characteristics of this group it has been suggested that cardiac magnetic resonance (CMR) imaging can more fully delineate MINOCA from other causes of elevated troponin, such as myocarditis, spontaneous coronary artery dissection, coronary embolization [26], and Takotsubo syndrome [30]. This is due to the ability of CMR to identify and quantify myocardial scar. In Takotsubo syndrome, a condition also highly prevalent in women [31], CMD may play a localized role at least in some cases [32,33].

As previously mentioned, CMD can also be present in patients with flow-limiting lesions in the epicardial coronary arteries. In fact, abnormal microvascular function is thought to precede the development of obstructive epicardial coronary artery disease [34] and may compound the extent of myocardial ischemia [19]. One important consideration is that the presence of CMD in patients with obstructive epicardial coronary artery disease may result in an underestimation of epicardial artery lesion severity when evaluated invasively by fractional flow reserve. In one study, investigators reported that in patients with CMD, the values obtained using fractional flow reserve to identify flow-limiting epicardial artery stenoses were higher than in patients with no evidence of CMD [35]. Not only can this lead to deferred revascularization of an epicardial lesion that is flow-limiting but may also explain why some patients have persistent ischemic symptoms even after "technically" successful revascularization of epicardial artery lesions.

In addition to being a primary driving force in INOCA, ANOCA, and MINOCA, there are many other heart-related conditions where CMD is a bystander, but may play a pathologic role. Systemic hypertension (without angina or signs of ischemia) [36], non-ischemic cardiomyopathy and infiltrative cardiomyopathies [37], diabetic cardiomyopathy [38], hypertrophic cardiomyopathy [39–42], aortic stenosis [43,44], and other disorders, such as HIV [45], and chemotherapy-associated cardiomyopathy are associated with CMD [46] (Table 1). Importantly, the bystander presence of CMD in these conditions is associated with worse outcomes. For example, the presence of CMD as measured by

Table 1
The spectrum of coronary microvascular dysfunction in heart disease.

CMD as primary driver of pathology
Angina with no obstructive coronary arteries
Ischemia with non-obstructive coronary artery disease
Myocardial infarction with non-obstructed coronary arteries
CMD as "innocent" bystander
Aortic stenosis
Diabetic cardiomyopathy
Hypertensive heart disease
Hypertrophic cardiomyopathy
HIV-associated cardiovascular disease
Chemotherapy-induced cardiomyopathy
Heart failure with preserved ejection fraction
Non-ischemic and infiltrative cardiomyopathy

decreased CFR in patients with hypertrophic cardiomyopathy is a strong and independent predictor of adverse left ventricular remodeling, left ventricular dysfunction, and adverse clinical outcomes including death [39–42]. Histologic studies have shown abnormalities of the coronary microvasculature in HCM including smaller lumen and decreased capillary density [47,48]. CFR is also decreased in aortic stenosis and is related to the severity of the stenotic valve orifice [43]. In this patient population, CMD may promote myocardial fibrosis and left ventricular dysfunction. In one study of patients with severe aortic stenosis undergoing transcatheter aortic valve replacement, CFR improved after the valve was replaced [44]. In hypertensive heart disease, a highly prevalent condition [49], pathologic changes associated with left ventricular hypertrophy include changes in the extracellular matrix, increased size of cardiomyocytes, and derangement of the coronary microvasculature, and can lead to heart failure with a reduced or preserved ejection fraction [50]. Recent data suggest that CMD leading to ischemia and fibrosis plays an important role in the pathophysiology driving heart failure with preserved ejection fraction (HFpEF), a condition associated with significant morbidity and mortality [51,52]. Decreased coronary blood flow as assessed by coronary reactivity testing is associated with the presence of diastolic dysfunction in patients with HFpEF and a 5-fold increased rate of hospitalization for heart failure exacerbation [51]. Whether CMD-associated ischemia leads to diffuse myocardial fibrosis, diastolic dysfunction and HFpEF is currently being studied in the NIH-funded Women's Ischemia Syndrome Evaluation Mechanisms of Coronary Microvascular Dysfunction Leading to Pre-Heart Failure with Preserved Ejection fraction (WISE preHFrEF) project (ClinicalTrials.gov NCT#03876223).

In the early stages of diabetic cardiomyopathy structural and functional abnormalities of the microvasculature are present that result in impaired myocardial perfusion and subsequent myocardial fibrosis [38]. In these patients, the presence of CMD among diabetics without flow-limiting epicardial stenoses was associated with at least as high and possibly higher rates of cardiac death compared to nondiabetic patients with known obstructive coronary artery disease [53]. Whether CMD is the primary pathologic driver of non-ischemic cardiomyopathy and infiltrative cardiomyopathies (such as Fabry's disease and amyloidosis) or if it is a bystander is unclear [37]. Regardless, the presence of CMD is associated with worse clinical outcomes including heart failure and death and could represent a focus of therapy for patients with these cardiomyopathies [37]. Endothelial dysfunction plays an important role in early cardiac transplant vasculopathy. In one study of heart transplant recipients, investigators reported significant epicardial coronary artery vasoconstriction and increased coronary blood flow in response to acetylcholine one year after transplantation. These patients had normal coronary flow reserve and no angiographic evidence of transplant vasculopathy [54]. Lastly, in people living with HIV, death due to cardiovascular disease has increased and CMD may play an important role [45]. Data suggest that CMD may be more common in HIV patients compared to those without HIV but with similar traditional cardiac risk factors [45]. The coronary microvasculature, therefore, could serve as a novel target for HIV-associated cardiovascular disease [45].

Patients with chronic inflammatory and autoimmune rheumatic disorders such as systemic lupus erythematosus and rheumatoid arthritis, are at increased risk for adverse cardiac events and CMD plays a crucial role in this pathophysiology. A combination of chronic inflammation and oxidative stress results in endothelial dysfunction and capillary rarefaction resulting in microvascular and macrovascular dysfunction [55]. In these patients, reduced CFR is common and is a major cause of chest pain in the absence of epicardial coronary artery disease [56]. CMD has been reported in nearly half of patients with systemic lupus erythematosus with suspected INOCA [57]. In this patient population, microvascular dysfunction is present in multiple organs including the heart, kidneys, lungs, and skin. This underscores an intriguing hypothesis that suggests microvascular dysfunction of the heart is an expression of a systemic illness that worsens with age and is accelerated by vascular risk factors. Blindness, small vessel disease of the brain, pulmonary hypertension, renal failure, and peripheral arterial disease are all conditions where microvascular dysfunction plays a key role [58].

4. Diagnosis

Consensus opinion from the Coronary Vasomotion Disorders International Study Group (COVADIS) suggests that more definitive testing for CMD should be pursued if the patient fulfills the following criteria: (1) presence of symptoms suggestive of myocardial ischemia; (2) objective documentation of myocardial ischemia; (3) absence of obstructive coronary artery disease (defined as <50 % coronary diameter reduction and/or fractional flow reserve >0.80); and (4) confirmation of a reduced coronary blood flow reserve and/or inducible microvascular spasm [59]. Currently diagnostic techniques involve both non-invasive and invasive modalities, each with its own inherent risks and benefits. Non-invasive methods to assess for CMD include transthoracic doppler echocardiography (TTDE) [60], positron emission tomography (PET) [18], CMR [61], and myocardial first-pass computed tomography (CT) [62]. PET is considered the reference standard in non-invasive testing for CMD. It measures myocardial perfusion reserve (MPR) by quantifying myocardial blood flow (MBF) at rest and at maximal hyperemia with an MPR < 2 considered as diagnostic of CMD. TTDE uses a pulsed-wave doppler focused on the mid left anterior descending coronary artery territory to calculate the coronary flow velocity ratio, and a value <2–2.5 suggests impaired microvascular function. This modality, however, is associated with technical pitfalls and requires a steep training curve. CMR measures myocardial perfusion reserve index and provides excellent anatomical visualization of the heart but it not an option in patients with contra-indications and difficult for those with claustrophobia. A major limitation to all these non-invasive tests is that acetylcholine cannot be used to test endothelial function.

Invasive coronary reactivity testing in the cardiac catheterization laboratory offers the benefit of identifying the presence of both abnormal vasodilation and constriction pathways. The ratio between coronary blood flow at maximal pharmacologic stress and at rest (coronary flow reserve) can be measured. Newer catheter-based invasive methods of assessing for CMD have allowed for more direct evaluation of the coronary microvasculature [63]. Despite the availability of an array of invasive and non-invasive diagnostic techniques, a significant number of patients with CMD remain undiagnosed. Circulating biomarkers in CMD to diagnose and follow response to therapy is a promising area of research and may allow point of care testing in a wide patient population from a simple blood draw [64,65].

5. Management

Medications prescribed for secondary prevention for coronary artery disease and conventional anti-anginal medications have been studied in CMD [66]. In general, these studies are small, short-term pilot studies, with the limitations associated with this type of design. Nonetheless, regimens that include a potent statin in conjunction with maximally tolerated doses of angiotensin-converting enzyme inhibitors (or angiotensin receptor blockers if intolerant) have been associated with amelioration of symptoms and improved microvascular function [67]. In an early study published in 1999, treatment with the beta-blocker, atenolol, resulted in a statistically significant reduction in the number of anginal episodes and was associated with improved quality of life [68]. Vasodilatory beta blockers such as nebivolol likely improve symptoms through activation of the eNOS pathway or preservation of nitric oxide activity [69]. Calcium channel blockers can also contribute to management of CMD via a vasodilatory mechanism [70]. Nitrates have been shown to be most effective in reducing angina when used in combination with either a calcium-channel blocker or a beta-blocker

[71]. Treatment with ranolazine was found to improve CFR and decrease angina frequency [72,73].

It has been proposed that drugs that work against the effects of angiotensin II in the renin-angiotensin-aldosterone system can improve the endothelial dysfunction that drives CMD [74]. One study demonstrated that enalapril therapy reduced exercise-induced ischemia in patients with CMD [75]. In a substudy of WISE, subjects with coronary flow reserve <3.0 following adenosine were randomized to quinapril (80 mg) or placebo for 4 months. Compared to placebo, those randomized to quinapril not only had significantly increased coronary flow reserve on invasive testing, but also had a significant reduction in anginal symptoms [76].

More targeted drugs including endothelin receptor antagonists and rho-kinase inhibitors have also been studied [77]. In another randomized study, simvastatin therapy was shown to significantly improve endothelial function in CMD patients as measured by flow-mediated dilatation of the brachial artery compared to placebo [78]. Moreover, subjects randomized to simvastatin treatment had longer times to ST segment changes on stress testing compared to those randomized to placebo. Novel, non-medication-based therapies including spinal cord stimulation [79], and exercise training [80] have also been studied with positive effects. We refer the reader to the paper published by Bairey Merz and colleagues for a complete review of the current state of CMD treatment [81].

The Women's Ischemia Trial to Reduce Events in Non-Obstructive CAD (WARRIOR, ClinicalTrials.gov NCT#03417388) is a multi-center, prospective study randomizing women with symptoms of ischemia and non-obstructive CAD to usual care or intensive medical therapy including high-intensity statin, aspirin and maximally tolerated angiotensin-converting enzyme inhibitor/or angiotensin receptor blocker [82]. Results of this study will provide important information regarding response to treatment and long-term clinical outcomes to inform future guideline recommendations.

6. Future considerations

While much has been learned about CMD there are still many unanswered questions regarding its pathophysiology. Mechanistic studies are needed to define the extent of structural defects and the functional abnormalities in CMD. Results from these studies will not only help us better understand the pathophysiology driving CMD but may also identify possible targets for novel therapies. Future studies should include men and adolescents to better understand the natural history of this disease process, and other cardiac conditions where CMD is considered an “innocent” bystander but plays a pathologic role and is associated with adverse clinical outcomes. Recently, the concept of multiple organ microvascular dysfunction has been raised [17,58] and of particular interest CMD and cerebral small vessel disease [83]. Lastly, research focused on identification and validation of biomarkers and genetic polymorphisms may improve our ability to predict risk of developing CMD and to diagnose it sooner.

Funding

Department of Defense W81XWH-17-2-0030 (Pepine).

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.

References

[1] P.G. Camici, F. Crea, Coronary microvascular dysfunction, N. Engl. J. Med. 356 (2007) 830.
[2] M.T. Ayub, D. Kalra, Coronary microvascular dysfunction and the role of noninvasive cardiovascular imaging, Diagnostics (Basel) 10 (2020) 679.
[3] M.G.D. Buono, R.A. Montone, M. Camilli, et al., Coronary microvascular dysfunction across the spectrum of cardiovascular diseases: JACC state-of-the-art review, J. Am. Coll. Cardiol. 78 (2021) 1352.
[4] K. Kisler, A.R. Nelson, S.V. Rege, et al., Pericyte degeneration leads to neurovascular uncoupling and limits oxygen supply to brain, Nat. Neurosci. 20 (2017) 406.
[5] D.J. Duncker, R.J. Bache, Regulation of coronary blood flow during exercise, Physiol. Rev. 88 (2008) 1009.
[6] M.M. Brandt, C. Cheng, D. Merkus, et al., Mechanobiology of microvascular function and structure in health and disease: focus on the coronary circulation, Front. Physiol. 12 (2021), 771960.
[7] V.R. Taqueti, M.F.D. Carli, Coronary microvascular disease pathogenic mechanisms and therapeutic options: JACC state-of-the-art review, J. Am. Coll. Cardiol. 72 (2018) 2625.
[8] N. Waheed, S. Elias-Smale, W. Malas, et al., Sex differences in non-obstructive coronary artery disease, Cardiovasc. Res. 116 (2020) 829.
[9] M. Gulati, R.M. Cooper-DeHoff, C. McClure, et al., Adverse cardiovascular outcomes in women with nonobstructive coronary artery disease, Arch. Intern. Med. 169 (2009) 843.
[10] A. Faccini, J.C. Kaski, P.G. Camici, Coronary microvascular dysfunction in chronic inflammatory rheumatoid diseases, Eur. Heart J. 37 (2016) 1799.
[11] B.N. Weber, E. Stevens, L. Barrett, et al., Coronary microvascular dysfunction in systemic lupus erythematosus, J. Am. Heart Assoc. 10 (2021), e018555.
[12] S.E. Reis, R. Holubkov, A.J.C. Smith, et al., Coronary microvascular dysfunction is highly prevalent in women with chest pain in the absence of coronary artery disease: results from the NHLBI WISE study, Am. Heart J. 141 (2001) 735.
[13] A. Recio-Mayoral, J.C. Mason, J.C. Kaski, et al., Chronic inflammation and coronary microvascular dysfunction in patients without risk factors for coronary artery disease, Eur. Heart J. 30 (2009) 1837.
[14] G.L. Erre, G. Buscetta, P. Paliogiannis, et al., Coronary flow reserve in systemic rheumatic diseases: a systematic review and meta-analysis, Rheumatol. Int. 38 (2018) 1179.
[15] V.K. Sandhu, J. Wei, L.E.J. Thomson, et al., Five-year follow-up of coronary microvascular dysfunction and coronary artery disease in systemic lupus erythematosus: results from a community-based lupus cohort, Arthritis Care Res. 72 (2020) 882.
[16] A. Recio-Mayoral, O.E. Rimoldi, P.G. Camici, Inflammation and microvascular dysfunction in cardiac syndrome X patients without conventional risk factors for coronary artery disease, JACC Cardiovasc. Imaging 6 (2013) 660.
[17] C. Berry, N. Sidik, A.C. Pereira, et al., Small-vessel disease in the heart and brain: current knowledge, unmet therapeutic need, and future directions, J. Am. Heart Assoc. 8 (2019), e011104.
[18] V.R. Taqueti, B.M. Everett, V.L. Murthy, et al., Interaction of impaired coronary flow reserve and cardiomyocyte injury on adverse cardiovascular outcomes in patients without overt coronary artery disease, Circulation 131 (2015) 528.
[19] U. Sechtem, D. Brown, S. Godo, et al., Coronary microvascular dysfunction in stable ischaemic heart disease (non-obstructive coronary artery disease and obstructive coronary artery disease), Cardiovasc. Res. 116 (2020) 771.
[20] P. Ong, A. Athanasiadis, G. Borgulya, et al., High prevalence of a pathological response to acetylcholine testing in patients with stable angina pectoris and unobstructed coronary arteries, J. Am. Coll. Cardiol. 59 (2012) 655.
[21] Y. Wang, P.Y. Jia, B.J. Chen, et al., Evaluation of plasma thrombomodulin in patients with coronary slow flow, Cardiology 138 (2017) 141.
[22] A. Nowroozpoor, D. Gutterman, B. Safdar, Is microvascular dysfunction a systemic disorder with common biomarkers found in the heart, brain, and kidneys? — a scoping review, Microvasc. Res. 134 (2021), 104123.
[23] V.L. Murthy, M. Naya, V.R. Taqueti, et al., Effects of sex on coronary microvascular dysfunction and cardiac outcomes, Circulation 129 (2014) 2518.
[24] M. Reriani, A.J. Flammer, J. Li, et al., Microvascular endothelial dysfunction predicts the development of erectile dysfunction in men with coronary atherosclerosis without critical stenoses, Coron. Artery Dis. 25 (2014) 552.
[25] B.D. Johnson, L.J. Shaw, C.J. Pepine, et al., Persistent chest pain predicts cardiovascular events in women without obstructive coronary artery disease: results from the NIH-NHLBI-sponsored Women’s ischaemia syndrome evaluation (WISE) study, Eur. Heart J. 27 (2006) 1408.
[26] B. Safdar, E.S. Spatz, R.P. Dreyer, et al., Presentation, clinical profile, and prognosis of young patients with myocardial infarction with nonobstructive coronary arteries (MINOCA): results from the VIRGO study, J. Am. Heart Assoc. 7 (2018), e009174.
[27] G. Scalone, G. Niccoli, F. Crea, Editor’s choice- pathophysiology, diagnosis and management of MINOCA: an update, Eur. Heart J. Acute Cardiovasc. Care 8 (2019) 54.
[28] D. Planer, R. Mehran, E.M. Ohman, et al., Prognosis of patients with non-ST-segment-elevation myocardial infarction and nonobstructive coronary artery disease: propensity-matched analysis from the acute catheterization and urgent intervention triage strategy trial, Cir.c Cardiovasc. Interv. 7 (2014) 285.
[29] B. Lindahl, T. Baron, D. Erlinge, et al., Medical therapy for secondary prevention and long-term outcome in patients with myocardial infarction with nonobstructive coronary artery disease, Circulation 135 (2017) 1481.
[30] S. Pasupathy, R. Tavella, J.F. Beltrame, Myocardial infarction with nonobstructive coronary arteries (MINOCA): the past, present, and future management, Circulation 135 (2017) 1490.
[31] H. Patel, N.T. Aggarwal, A. Rao, et al., Microvascular disease and small-vessel disease: the nexus of multiple diseases of women, J. Women's Health (Larchmt) 29 (2020) 770.

[32] A.R. Lyon, R. Citro, B. Schneider, et al., Pathophysiology of takotsubo syndrome: JACC state-of-the-art review, J. Am. Coll. Cardiol. 77 (2021) 902.
[33] S. Y-Hassan, Coronary microvascular dysfunction in Takotsubo syndrome: cause or consequence, Am. J. Cardiovasc. Dis. 11 (2021) 184.
[34] D.D. Gutterman, D.S. Chabowski, A.O. Kadlec, et al., The human microcirculation: regulation of flow and beyond, Circ. Res. 118 (2016) 157.
[35] T.P. van de Hoef, F. Nolte, M. Echavarría-Pinto, et al., Impact of hyperaemic microvascular resistance on fractional flow reserve measurements in patients with stable coronary artery disease: insights from combined stenosis and microvascular resistance assessment, Heart 100 (2014) 951.
[36] T. Padro, O. Manfrini, R. Bugiardini, et al., ESC working group on coronary pathophysiology and microcirculation position paper on 'coronary microvascular dysfunction in cardiovascular disease', Cardiovasc. Res. 116 (2020) 741.
[37] P.E. Bravo, M.F.D. Carli, S. Dorbala, Role of PET to evaluate coronary microvascular dysfunction in non-ischemic cardiomyopathies, Heart Fail. Rev. 22 (2017) 455.
[38] G. Jia, M.A. Hill, J.R. Sowers, Diabetic cardiomyopathy: an update of mechanisms contributing to this clinical entity, Circ. Res. 122 (2018) 624.
[39] R. Krams, M.J. Kofflard, D.J. Duncker, et al., Decreased coronary flow reserve in hypertrophic cardiomyopathy is related to remodeling of the coronary microcirculation, Circulation 97 (1998) 230.
[40] I. Olivotto, F. Girolami, R. Sciagrà, et al., Microvascular function is selectively impaired in patients with hypertrophic cardiomyopathy and sarcomere myofilament gene mutations, J. Am. Coll. Cardiol. 58 (2011) 839.
[41] I. Olivotto, F. Cecchi, R. Gistri, et al., Relevance of coronary microvascular flow impairment to long-term remodeling and systolic dysfunction in hypertrophic cardiomyopathy, J. Am. Coll. Cardiol. 47 (2006) 1043.
[42] F. Cecchi, I. Olivotto, R. Gistri, et al., Coronary microvascular dysfunction and prognosis in hypertrophic cardiomyopathy, N. Engl. J. Med. 349 (2003) 1027.
[43] D. Garcia, P.G. Camici, L.G. Durand, et al., Impairment of coronary flow reserve in aortic stenosis, J. Appl. Physiol. 2009 (106) (1985) 113.
[44] E.M.A. Wiegerinck, T.P. van de Hoef, M.C. Rolandi, et al., Impact of aortic valve stenosis on coronary hemodynamics and the instantaneous effect of transcatheter aortic valve implantation, Circ. Cardiovasc. Interv. 8 (2015), e002443.
[45] L. Rethy, M.J. Feinstein, A. Sinha, et al., Coronary microvascular dysfunction in HIV: a review, J. Am. Heart Assoc. 9 (2020), e014018.
[46] S.N. Hader, N. Zinkevich, L.E.N. Toro, et al., Detrimental effects of chemotherapy on human coronary microvascular function, Am. J. Physiol. Heart Circ. Physiol. 317 (2019) H705.
[47] M. Tanaka, H. Fujiwara, T. Onodera, et al., Quantitative analysis of narrowings of intramyocardial small arteries in normal hearts, hypertensive hearts, and hearts with hypertrophic cardiomyopathy, Circulation 75 (1987) 1130.
[48] B. Johansson, S. Mörner, A. Waldenström, et al., Myocardial capillary supply is limited in hypertrophic cardiomyopathy: a morphological analysis, Int. J. Cardiol. 126 (2008) 252.
[49] K.T. Mills, A. Stefanescu, J. He, The global epidemiology of hypertension, Nat Rev Nephrol 16 (2020) 223.
[50] M.H. Drazner, The progression of hypertensive heart disease, Circulation 123 (2011) 327.
[51] V.R. Taqueti, S.D. Solomon, A.M. Shah, et al., Coronary microvascular dysfunction and future risk of heart failure with preserved ejection fraction, Eur. Heart J. 39 (2018) 840.
[52] A. Sinha, H. Rahman, A. Webb, et al., Untangling the pathophysiologic link between coronary microvascular dysfunction and heart failure with preserved ejection fraction, Eur. Heart J. 42 (2021) 4431.
[53] V.L. Murthy, M. Naya, C.R. Foster, et al., Association between coronary vascular dysfunction and cardiac mortality in patients with and without diabetes mellitus, Circulation 126 (2012) 1858.
[54] R.M. Mills, J.M. Billett, W.W. Nichols, Endothelial dysfunction early after heart transplantation. Assessment with intravascular ultrasound and doppler, Circulation 86 (1992) 1171.
[55] R.E. Konst, T.J. Guzik, J.C. Kaski, et al., The pathogenic role of coronary microvascular dysfunction in the setting of other cardiac or systemic conditions, Cardiovasc. Res. 116 (2020) 817.
[56] E. Zanatta, C. Colombo, G. D'Amico, et al., Inflammation and coronary microvascular dysfunction in autoimmune rheumatic diseases, Int. J. Mol. Sci. 20 (2019) 5563.
[57] A.S. Manchanda, A.C. Kwan, M. Ishimori, et al., Coronary microvascular dysfunction in patients with systemic lupus erythematosus and chest pain, Front. Cardiovasc. Med. 9 (2022), 867155.
[58] D.S. Feuer, E.M. Handberg, B. Mehrad, et al., Microvascular dysfunction as a systemic disease: a review of the evidence, Am. J. Med. 135 (2022) 1059–1068.
[59] P. Ong, P.G. Camici, J.F. Beltrame, et al., International standardization of diagnostic criteria for microvascular angina, Int. J. Cardiol. 250 (2018) 16.
[60] N.D. Mygind, M.M. Michelsen, A. Pena, et al., Coronary microvascular function and cardiovascular risk factors in women with angina pectoris and no obstructive coronary artery disease: the iPOWER study, J. Am. Heart Assoc. 5 (2016), e003064.
[61] G.A. Lanza, A. Buffon, A. Sestito, et al., Relation between stress-induced myocardial perfusion defects on cardiovascular magnetic resonance and coronary microvascular dysfunction in patients with cardiac syndrome X, J. Am. Coll. Cardiol. 51 (2008) 466.
[62] V.L. Murthy, M.F.D. Carli, Non-invasive quantification of coronary vascular dysfunction for diagnosis and management of coronary artery disease, J. Nucl. Cardiol. 19 (2012) 1060.
[63] Y. Saito, T. Nishi, K. Kato, et al., Resistive reserve ratio and microvascular resistance reserve in patients with coronary vasospastic angina, Heart Vessel. 37 (2022) 1489, https://doi.org/10.1007/s00380-022-02051-w.
[64] A.A. Eve, E. Tunc, Y.J. Liu, et al., Identification of circulating diagnostic biomarkers for coronary microvascular disease in postmenopausal women using machine-learning techniques, Metabolites 11 (2021) 339.
[65] E. Rocco, M.C. Grimaldi, A. Maino, et al., Advances and challenges in biomarkers use for coronary microvascular dysfunction: from bench to clinical practice, J. Clin. Med. 11 (2022) 2055.
[66] C.N.B. Merz, C.J. Pepine, H. Shimokawa, et al., Treatment of coronary microvascular dysfunction, Cardiovasc. Res. 116 (2020) 856–870.
[67] C. Pizzi, O. Manfrini, F. Fontana, et al., Angiotensin-converting enzyme inhibitors and 3-hydroxy-3-methylglutaryl coenzyme a reductase in cardiac syndrome X: role of superoxide dismutase activity, Circulation 109 (2004) 53.
[68] G.A. Lanza, G. Colonna, V. Pasceri, et al., Atenolol versus amlodipine versus isosorbide-5-mononitrate on anginal symptoms in syndrome X, Am. J. Cardiol. 84 (1999) 854.
[69] A. Sinha, H. Rahman, D. Perera, Coronary microvascular disease: current concepts of pathophysiology, diagnosis and management, Cardiovasc. Endocrinol. Metab. 10 (2020) 22.
[70] K. Ohba, S. Sugiyama, H. Sumida, et al., Microvascular coronary artery spasm presents distinctive clinical features with endothelial dysfunction as nonobstructive coronary artery disease, J. Am. Heart Assoc. 1 (2012), e002485.
[71] J.C. Kaski, G.M.C. Rosano, P. Collins, et al., Cardiac syndrome X: clinical characteristics and left ventricular function: long-term follow-up study, J. Am. Coll. Cardiol. 25 (1995) 807.
[72] C.N.B. Merz, E.M. Handberg, C.L. Shufelt, et al., A randomized, placebo-controlled trial of late na current inhibition (ranolazine) in coronary microvascular dysfunction (CMD): impact on angina and myocardial perfusion reserve, Eur. Heart J. 37 (2016) 1504.
[73] C.A. Rambarat, I.Y. Elgendy, E.M. Handberg, et al., Late sodium channel blockade improves angina and myocardial perfusion in patients with severe coronary microvascular dysfunction: women's ischemia syndrome evaluation-coronary vascular dysfunction ancillary study, Int. J. Cardiol. 276 (2019) 8.
[74] G.A. Lanza, F. Crea, Primary coronary microvascular dysfunction: clinical presentation, pathophysiology, and management, Circulation 121 (2010) 2317.
[75] J.C. Kaski, G. Rosano, S. Gavrielides, et al., Effects of angiotensin-converting enzyme inhibition on exercise-induced angina and ST segment depression in patients with microvascular angina, J. Am. Coll. Cardiol. 23 (1994) 652.
[76] D.F. Pauly, B.D. Johnson, R.D. Anderson, et al., In women with symptoms of cardiac ischemia, nonobstructive coronary arteries, and microvascular dysfunction, angiotensin-converting enzyme inhibition is associated with improved microvascular function: a double-blind randomized study from the National Heart, lung and blood institute Women's ischemia syndrome evaluation (WISE), Am. Heart J. 162 (2011) 678.
[77] M. Reriani, E. Raichlin, A. Prasad, et al., Long-term administration of endothelin receptor antagonist improves coronary endothelial function in patients with early atherosclerosis, Circulation 122 (2010) 958.
[78] E. Fábián, A. Varga, E. Picano, et al., Effect of simvastatin on endothelial function in cardiac syndrome X patients, Am. J. Cardiol. 94 (2004) 652.
[79] A. Sestito, G.A. Lanza, D.L. Pera, et al., Spinal cord stimulation normalizes abnormal cortical pain processing in patients with cardiac syndrome X, Pain 139 (2008) 82.
[80] B.E. Eriksson, R. Tyni-Lennè, J. Svedenhag, et al., Physical training in syndrome X: physical training counteracts deconditioning and pain in syndrome X, J. Am. Coll. Cardiol. 36 (2000) 1619.
[81] C.N.B. Merz, C.J. Pepine, H. Shimokawa, et al., Treatment of coronary microvascular dysfunction, Cardiovasc. Res. 116 (2020) 856.
[82] E.M. Handberg, C.N.B. Merz, R.M. Cooper-Dehoff, et al., Rationale and design of the Women's ischemia trial to reduce events in nonobstructive CAD (WARRIOR) trial, Am. Heart J. 237 (2021) 90.
[83] C.J. Pepine, C.N. Bairey Merz, Heart and brain interactions: Is small vessel disease a link? Eur. Heart J. (2022). In press.