Arteriosclerosis, Thrombosis, and Vascular Biology

BRIEF REVIEW

Coronary Microvascular Dysfunction

Shigeo Godo, Akira Suda, Jun Takahashi, Satoshi Yasuda, Hiroaki Shimokawa

ABSTRACT: Over the past couple of decades, accumulating evidence has shown that structural and functional abnormalities of coronary microvasculature are highly prevalent, associated with adverse clinical outcomes in patients with various cardiovascular diseases. The term coronary microvascular dysfunction (CMD) has been coined to refer to this clinical condition and is increasingly recognized as an important clinical entity in many clinical settings. The potential mechanisms of CMD appear to be heterogenous, including enhanced coronary vasoconstrictive reactivity at microvascular level, impaired endothelium-dependent and independent coronary vasodilator capacities, and increased coronary microvascular resistance secondary to structural factors. Recent experimental and clinical studies have highlighted emerging modulators of vascular functions, vital insight into the pathogenesis of cardiovascular diseases associated with CMD, and potential therapeutic interventions to CMD with major clinical implications. In this article, we will briefly review the current progress on pathophysiology, molecular mechanisms, and clinical management of CMD from bench to bedside.

Key Words: cardiovascular diseases ■ coronary artery disease ■ endothelium ■ humans ■ microvessels

A growing body of evidence has underscored the importance of coronary microvascular dysfunction (CMD), which manifests as the structural and functional abnormalities of coronary microvasculature, in a variety of cardiovascular diseases.[1] The prevalence of CMD is higher than ever thought in many clinical settings,[2–4] and its presence is associated with worse clinical outcomes, especially when accompanied by myocardial ischemia[5] or nonsignificant coronary artery disease (CAD).[6] Previous studies exclusively targeted structural and functional abnormalities of epicardial coronary arteries of patients with CAD because these arteries are easily visible on coronary angiography and readily amenable to procedural intervention, such as percutaneous coronary intervention (PCI) and coronary artery bypass grafting. A nationwide large-scale cohort study in the United States enrolling a total of 12 062 081 coronary revascularizations was performed to assess the contemporary trends in the characteristics and outcomes of patients with CAD.[7] Notably, this study revealed that risk-adjusted mortality significantly decreased after coronary artery bypass grafting but not after PCI across all clinical indications.[7] In line with these findings, a limit to the benefit of PCI versus optimal medical therapy in stable CAD has been replicated by the results of the 2 recent landmark clinical trials, the ORBITA trial (Objective Randomized Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina)[8] and the ISCHEMIA trial (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches).[9] Although these trials did not directly address coronary microvascular function, the questionable benefit of PCI in patients with stable CAD is suggestive of the importance of coronary microvascular physiology; it may be speculated that CMD contributes to myocardial ischemia even after successful revascularization of significant epicardial coronary stenosis. The underlying mechanisms behind CMD appear to be multiple and complex, including several structural and functional alterations in the coronary microcirculation that often coexist in various combinations.[3,10–13] In this review, we highlight the current advances in the research on CMD and underlying mechanisms and some updates on endothelial modulation of vascular tone from bench to bedside.

Correspondence to: Hiroaki Shimokawa, MD, PhD, Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574. Email shimo@cardio.med.tohoku.ac.jp

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Nonstandard Abbreviations and Acronyms

ACE2	angiotensin-converting enzyme 2
ADAM17	a disintegrin and metalloprotease
CAD	coronary artery disease
CMD	coronary microvascular dysfunction
COVID-19	coronavirus disease 2019
EDH	endothelium-dependent hyperpolarization
ENDOFIND	Endothelial Function-Guided Management in Patients With Non-Obstructive Coronary Artery Disease
FKBP12	FK506-binding protein 12
ISCHEMIA	International Study of Comparative Health Effectiveness With Medical and Invasive Approaches
JUPITER	Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
MPO	myeloperoxidase
mTOR	mammalian target of rapamycin
ORBITA	Objective Randomized Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina
PCI	percutaneous coronary intervention
PVAT	perivascular adipose tissue
VSMC	vascular smooth muscle cells
WARRIOR	Women's Ischemia Trial to Reduce Events in Non-Obstructive CAD
WISE	Women's Ischemic Syndrome Evaluation

Highlights

- Structural and functional abnormalities of coronary microvasculature, referred to as coronary microvascular dysfunction, are highly prevalent in association with adverse clinical outcomes in patients with various cardiovascular diseases.
- The potential mechanisms of coronary microvascular dysfunction appear to be heterogenous, including enhanced coronary vasoconstrictive reactivity at microvascular level, impaired endothelium-dependent and independent coronary vasodilator capacities, and increased coronary microvascular resistance secondary to structural factors.
- Recent research has highlighted emerging modulators of vascular functions, novel insight into the pathogenesis of cardiovascular diseases associated with coronary microvascular dysfunction, and potential therapeutic interventions to coronary microvascular dysfunction with major clinical implications.

PATHOPHYSIOLOGY OF CMD AND ENDOTHELIAL MODULATION OF VASCULAR TONE

The potential mechanisms of CMD appear to be heterogenous, encompassing enhanced coronary vasoconstrictive reactivity at microvascular level (eg, coronary microvascular spasm), impaired endothelium-dependent and independent coronary vasodilator capacities, and increased coronary microvascular resistance secondary to structural factors (eg, luminal narrowing, vascular remodeling, vascular rarefaction, and extramural compression; Figure 1).[1] Coronary microvascular spasm is defined as reproduction of angina symptoms, ischemic ECG changes, but no epicardial spasm during intracoronary acetylcholine provocation testing.[14] The major mechanisms of coronary microvascular spasm include Rho kinase–induced myosin light-chain phosphorylation,[15] increased production of vasoconstrictive mediators (eg, serotonin),[16] and inflammatory conditions in the coronary microvasculature[17] with resultant enhanced coronary vasoconstrictive reactivity. A comprehensive invasive assessment of CMD by functional coronary angiography is safe, feasible, and of diagnostic value to better differentiate between endothelium-dependent and independent CMD.[3,10,13,18] An autopsy study by de Waard et al[19] of patients without structural or infiltrative myocardial disease who had undergone coronary angiography within 2 years before death was performed to examine whether structural alterations occurred in the coronary microcirculation downstream of epicardial coronary stenoses. The findings showed no microcirculatory remodeling distal to noncritical stenoses, validating the rationale for invasive or noninvasive physiology-derived indices, such as fractional flow reserve, and that microvascular resistance at maximal hyperemia is similar regardless of the presence or absence of a stenosis.[19,20]

The endothelium plays a pivotal role in modulating vascular tone by synthesizing and liberating endothelium-derived relaxing factors, including vasodilator prostaglandins, NO, and endothelium-dependent hyperpolarization (EDH) factors in a distinct vessel size–dependent manner; NO predominantly mediates vasodilatation of relatively large, conduit vessels (eg, epicardial coronary arteries), while EDH factors in small resistance vessels (eg, coronary microvessels; Figure 1).[21,22] Endothelium-dependent CMD can be attributed to reduced production or action of these relaxing mediators. Among them, hydrogen peroxide is one of the major EDH factors in various vascular beds including human coronary arteries.[1,23] For example, by means of a unique bioassay method, a previous study showed that hydrogen peroxide derived from the beating heart caused the metabolic coronary microvascular dilation in vivo.[24] It is conceivable that impaired hydrogen peroxide/EDH factor–mediated vasodilatation is involved in

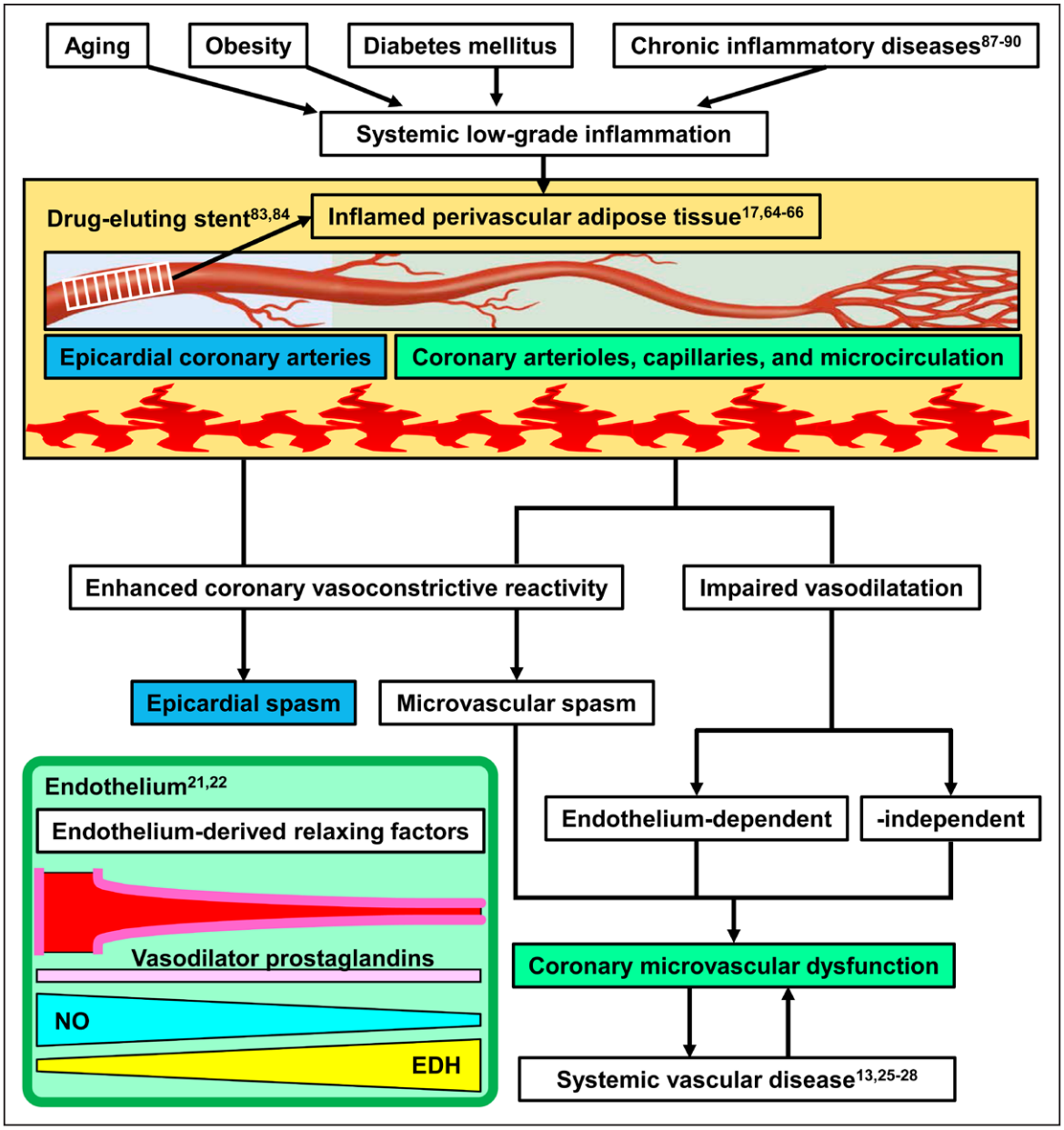

Figure 1. Mechanisms of coronary microvascular dysfunction and endothelial modulation of vascular tone in a vessel size–dependent manner.
Each number corresponds to the reference. EDH indicates endothelium-dependent hyperpolarization.

the pathogenesis of CMD in light of its potent vasodilator properties in coronary resistance vessels where EDH factor–mediated responses become relatively dominant to NO-mediated relaxations.[1,23]

CMD AS A SYSTEMIC VASCULAR DISEASE BEYOND THE HEART

Recent studies have demonstrated that patients with coronary vasomotion abnormalities are often accompanied by peripheral endothelial dysfunction as well, where CMD manifests as systemic vascular dysfunction beyond the heart (Figure 1).[13,25–28] Al-Badri et al[26] invasively and simultaneously measured acetylcholine-induced endothelium-dependent and adenosine- or sodium nitroprusside–induced endothelium-independent vascular reactivity of coronary and femoral arteries and showed a modest but significant correlation in endothelial functional changes between the coronary and peripheral circulations. In line with these observations, we have demonstrated that both NO- and EDH-mediated digital vasodilatations were markedly impaired in patients with microvascular angina,[13] which was diagnosed by the gold standard coronary reactivity testing.[14] Coronary endothelial dysfunction is associated with impaired high-density lipoprotein function,[29] which is modulated by a genetic

polymorphism in the haptoglobin gene.[30] Specifically, high-density lipoprotein function is markedly impaired in diabetic patients who carry haptoglobin 2-2 genotype.[30] Based on these observations, Asleh et al[31] demonstrated that the haptoglobin 2-2 phenotype was associated with coronary endothelial dysfunction at both epicardial and microvascular levels in patients with chest pain and angiographically normal coronary arteries or mild nonobstructive CAD (<30% diameter stenosis), especially in those with diabetes. This association might be related to the increased amount of hemoglobin bound to high-density lipoprotein through haptoglobin 2-2, which contributes to impaired NO bioavailability and dysfunctional high-density lipoprotein.[31] Notably, the deleterious impact of haptoglobin 2-2 on endothelial dysfunction was more prominent in the coronary microcirculation than in the epicardial coronary artery.[31] These results imply that coronary microvascular endothelial dysfunction may precede epicardial coronary endothelial dysfunction, driven by oxidative stress and inflammation in the early stage of CAD. In agreement with this notion, an animal study by Plaza et al[32] showed that focal vascular inflammation accelerates the development and progression of atherosclerosis in remote arteries. Briefly, a focal mechanical injury-induced persistent aortic inflammation in ApoE-knockout mice accelerated atherosclerosis in the remote brachiocephalic artery associated with elevated levels of serum interleukin-6.[32] This inflammatory cascade was mitigated by the treatment with pravastatin or minocycline, both of which have anti-inflammatory properties.[32] Dou et al[33] showed that aging and obesity were associated with a significant decline in the expression of caveolin-1, an inhibitory regulator of ADAM17 (a disintegrin and metalloprotease). The dissociation of ADAM17 from its inhibitory interaction with caveolin-1 induced phenotype transition of perivascular adipose tissue (PVAT) into a proinflammatory state by increasing ADAM17 activity and soluble tumor necrosis factor release in adipose tissue, leading to impaired bradykinin-evoked endothelium-dependent vasodilatation of human coronary arterioles and thereby the development of remote CMD.[33] To the contrary, given a recent study showing that caveolin-1 deficiency attenuated vascular inflammation and atherosclerosis by activating endothelial autophagy,[34] how to modulate caveolin-1 to benefit patients awaits further investigation. Taken together, it is conceivable that patients with endothelium-dependent CMD may benefit from early aggressive medical management for restoring endothelial function and underlying risk factors upon detection of systemic endothelial dysfunction.

SEX DIFFERENCES IN CMD

Multiple mechanisms appear to contribute to the sex differences[35] in CMD, including differences in sex hormone effects, autonomic regulation, and susceptibility to proatherogenic mediators, such as oxidative stress, endothelin-1, and angiotensin II.[36] When considering interventions to endothelium-related CMD, it is important to note that among the aforementioned 3 endothelium-derived relaxing factors, EDH-mediated vasodilatation is more predominant in female resistance arteries as compared with male counterparts.[22] Considering the lower prevalence of obstructive CAD and higher prevalence of CMD in female patients with chest pain in the absence of obstructive CAD, the proper assessment and diagnosis of coronary functional rather than structural abnormalities should be encouraged, particularly in women.[36] Sullivan et al[37] revealed distinct sex differences in hemodynamic and microvascular mechanisms of mental stress–induced myocardial ischemia. Briefly, a more prominent peripheral microvascular dysfunction measured by peripheral arterial tonometry and a less pronounced hemodynamic role assessed by the rate-pressure product were associated with the development of metal stress–induced myocardial ischemia in women and vice versa in men.[37] These results support the role of stress-induced vasoconstriction in the pathogenesis of CMD particularly in women and provide a clue to develop sex-specific treatment for CMD. The results of the WISE study (Women's Ischemic Syndrome Evaluation) funded by the National Heart, Lung, and Blood Institute have provided important insight into the clinical characteristics of ischemic heart disease in women.[38,39] The major findings of the WISE study are that CMD is highly prevalent and responsible for myocardial ischemia in patients with chest pain who are found to have no obstructive CAD and that the diagnostic evaluation of CMD is important using invasive or noninvasive coronary reactivity testing.[38,39] AlBadri et al[40] added another layer of evidence to substantiate the role of CMD in the increased risk for adverse cardiovascular events in this population; higher levels of ultra-high-sensitivity cardiac troponin I were associated with both endothelium-dependent and independent CMD in women with symptoms or signs of myocardial ischemia but no obstructive CAD.

EMERGING MODULATORS OF MICROVASCULAR FUNCTION

Molecular Modulators

Arginase

Arginase I is constitutively expressed in the coronary microvascular endothelial cells and inhibits the production of NO by competing with endothelial NO synthase for the common substrate L-arginine.[41] Masi et al[42] showed that endothelium-dependent, NO-mediated relaxations of subcutaneous small arteries were impaired by arginase in obese subjects; however, the influence of arginase on endothelial function was lessened by aging because of vascular oxidative stress and irreversible

vascular remodeling. These results indicate that early therapeutic interventions aimed at arginase activity are warranted to prevent obesity- and aging-related endothelial dysfunction and vascular remodeling. By contrast, in a diabetic mouse model, genetic ablation of endothelial arginase-1 had a neutral effect on vasomotor function of resistance arteries.[43] In another porcine model of chronic myocardial ischemia, CMD developed independently of the activity and expression of arginase I.[44] Given that coronary vascular resistance is predominantly determined by the prearterioles and arterioles[45] where the effect of EDH-mediated relaxations on vascular tone surpasses that of NO-mediated relaxations,[46] it is important to consider the vessel size–dependent contribution of NO and EDH factors for the treatment of CMD. Taken together, endotyping patients with CMD based on the underlying mechanism of the disorder may be crucial to tailor the most appropriate treatment and to identify those who benefit from arginase inhibition (Figure 2).

Calreticulin

Calreticulin is a calcium-binding chaperone that is highly expressed throughout the internal elastic lamina in small arteries.[47] Using tamoxifen-inducible, endothelium-specific, calreticulin-knockout mice, Biwer et al[47] revealed that nonendoplasmic reticulum pool of calreticulin in resistance mesenteric arteries played important roles in the regulation of intercellular calcium signaling between endothelial cells and vascular smooth muscle cell (VSMC), vasoreactivity, and thus blood pressure. The same group subsequently showed that endothelial calreticulin knockdown impaired carbachol-induced endothelium-dependent vasodilatation of resistance mesenteric arteries associated with endoplasmic reticulum stress in aged mice.[48] In light of the notion that CMD is a systemic vascular disease beyond the heart, calreticulin may be a potential therapeutic target for CMD (Figure 2).

Flavoring Additives

The growing use of vaping products has been a public health issue in general and implicated in the pathogenesis of microvascular disease in particular.[49,50] Ciftci et al[49] showed that smoking mentholated cigarettes significantly reduced coronary flow reserve to the same extent of regular cigarettes. Fetterman et al[51] showed that flavoring additives in electronic cigarettes and other tobacco products, such as menthol and eugenol, at low concentrations likely to be achieved in vivo, increased the expression of the proinflammatory cytokine interleukin-6 and decreased the production of NO in human endothelial cells, possibly leading to endothelial dysfunction and cardiovascular toxicity. Carnevale et al[52] showed that electronic cigarette use was associated with detrimental effects on flow-mediated dilatation, oxidative stress, and NO bioavailability, while Kerr et al[50] showed a counterintuitive result that reactive hyperemia index—an index of microvascular endothelial function assessed via peripheral artery tonometry—increased acutely after electronic cigarette use. In the latter study, however, decreased pulse wave amplitudes were suggestive of an acute vasoconstrictive response in the microvasculature following electronic cigarette smoke (Figure 2).[50]

Tissue Modulators

Glycocalyx

Endothelial glycocalyx serves as a vascular barrier at the border of the endothelium and blood with important roles in preserving physiological endothelial functions, including anticoagulation, mechanotransduction, and shear stress–mediated NO production.[53] The function of glycocalyx can be evaluated by measuring its antithrombogenic capacity in vitro.[54] In diabetes, hyperglycemia causes damage to endothelial glycocalyx with resultant endothelial dysfunction, whereas preserving endothelial glycocalyx by inhibiting the function of a major circulating hyaluronidase HYAL1 may be a promising therapeutic target to prevent diabetic micro- and macrovascular complications.[53] MPO (myeloperoxidase) is a heme-containing peroxidase that promotes oxidative stress and inflammatory responses in the vascular wall in various diseased conditions. Cheng et al[55] showed that a pharmacological inhibition of MPO attenuated inflammation-driven endothelial dysfunction in 3 different mouse models of vascular inflammation and atherosclerosis. Manchanda et al[56] revealed that MPO interacted with heparan sulfate side chains to cause neutrophil-dependent shedding of syndecan-1—a core protein of endothelial glycocalyx—and thereby disrupted the structure of endothelial glycocalyx. Moreover, using gain- and loss-of-function genetic mouse models and obese human samples, Fancher et al[57] revealed that obesity-induced impaired flow sensitivity of endothelial inwardly rectifying K^+ channels was associated with glycocalyx disruption and obesity-induced endothelial dysfunction of resistance arteries. Furthermore, Wang et al[58] showed that physiological laminar shear stress on the endothelium regulated the biosynthesis of hyaluronan—a major structural component of the endothelial glycocalyx. This mechanism maintains a thick glycocalyx layer on the surface of the endothelium to keep endothelial functions, such as antipermeability, anti-inflammatory, and antithrombotic properties (Figure 2).[58]

Vascular Smooth Muscle Cells

Along with endothelial dysfunction, VSMC dysfunction, like coronary artery spasm and VSMC remodeling, also serves as one of the major pathogenetic mechanisms of CMD.[1,59] Pannexin-1 has emerged as the physiological conduit that forms ATP-releasing channels to regulate vascular tone, highly expressed in endothelium and VSMC throughout the coronary artery tree.[60] Using a novel tamoxifen-inducible, VSMC-specific, caveolin-1 knockout mice, DeLalio et al[61] showed that colocalization

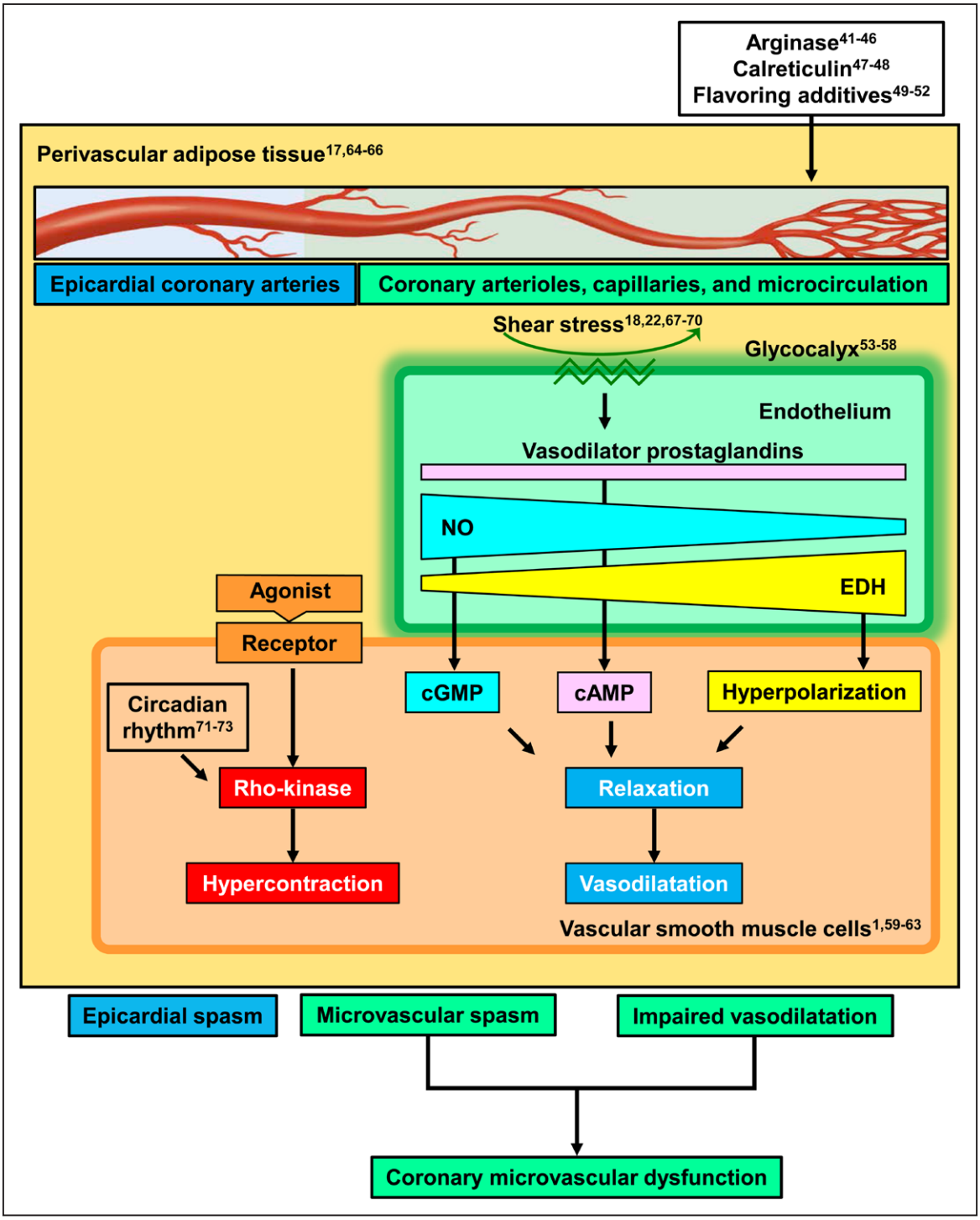

Figure 2. Emerging modulators of microvascular function.
Each number corresponds to the reference. EDH indicates endothelium-dependent hyperpolarization.

and functional coupling of pannexin-1 and caveolin-1 in VSMC caveolae of resistance arteries played important roles in the regulation of blood pressure via sympathetic-mediated ATP release and vasoconstriction without affecting endothelium-dependent relaxation to acetylcholine. Barrese et al[62] revealed a novel interaction in VSMC between sodium-myo-inositol transporter 1 and Kv7.4/Kv7.5 heteromeric channels that modulate arterial contractility; exposure to hypertonic medium increased the expression of sodium-myo-inositol transporter 1, which augmented vasorelaxation through the activation of Kv7.4/Kv7.5 channels. Such mechanisms may help explain hyperosmolarity-induced vasodilation in several vascular beds, including coronary arteries, as seen

in diabetes. Additionally, van der Horst et al[63] showed that Kv7 potassium channels played an important role in intravenous acetaminophen-induced vasodilatation and hypotension in the clinical settings (Figure 2).

Perivascular Adipose Tissue

Accumulating evidence has revealed the role of inflamed PVAT in the pathogenesis of coronary vasomotion abnormalities including CMD (Figure 1).[17] Briot et al[64] revealed the impact of senescence on the fatty acid handling and inflammatory response in microvascular endothelial cells of human adipose tissue; senescence induced a peroxisome proliferator–activated receptor gamma-dependent phenotypic change in endothelial cells from active fatty acid transporter toward proinflammatory activated cells. These mechanisms may underlie adipose tissue dysfunction in favor of inflammatory response associated with obesity and aging. Saxton et al[65] revealed 2 novel mechanisms by which PVAT exerted an anticontractile effect on resistance arteries; PVAT served as a releaser of adiponectin in a paracrine manner via β_3-adrenoceptor activation, as well as a reservoir for sympathetic nerve–derived noradrenaline, and thus prevented vasocontraction. Haynes et al[66] demonstrated the presence of endothelial-to-mesenchymal transition in obese human adipose tissue with resultant functional changes of endothelial cells, including impaired barrier function, increased migration, reduced proliferative capacity, and blunted angiogenic response. Along with the local effects of this transition in the adipose tissue microenvironment, dysfunctional endothelial cells were able to produce and release increased number of extracellular vesicles with inflammatory and immune activities, which might be disseminated in a paracrine or endocrine manner to cause endothelial dysfunction in remote vascular beds (Figure 2).[66]

Exogenous Modulators

Shear Stress

Shear stress serves as important physiological stimuli that make endothelial cells synthesize and liberate endothelium-derived relaxing factors to maintain vascular homeostasis.[22] In striking contrast to the atheroprotective effects of steady laminar or pulsatile shear stress, altered oscillatory or low shear stress with disturbed flow on the vascular wall accelerates atherogenesis through multiple mechanisms, including endothelial and VSMCs proliferation, inflammation, lipoprotein uptake, and leukocyte adhesion.[67,68] Recent studies have shown that endothelium-dependent CMD is associated with advanced plaque characteristics via low endothelial shear stress in the epicardial coronary artery, contributing to the development of epicardial coronary atherosclerosis, even though epicardial coronary lesions are located upstream to the microcirculation (Figure 2).[18,69,70]

Circadian Rhythm

Circadian rhythm is an internal biological clock that regulates numerous physiological processes in the body. We have previously showed that Rho kinase activity in circulating leukocytes of patients with vasospastic angina exhibited a marked circadian variation with a peak at early morning and that Rho kinase activity was associated with enhanced coronary vasoconstrictive reactivity in response to acetylcholine.[71] Speculatively, such circadian variation of Rho kinase activity may be a therapeutic consideration for a subset of patients with CMD because Rho kinase–induced myosin light-chain phosphorylation is a major mechanism of coronary microvascular spasm as well.[15] Low-dose aspirin administered at night but not in the morning is known to have a blood pressure–lowering effect in hypertensive patients. Chen et al[72] successfully reproduced the time-dependent hypotensive effect of aspirin in mice, however, unexpectedly, found no time-dependent effect of aspirin on the canonical clock genes expression or acetylation in the key organs of hypertension or on the urinary excretion of prostaglandins and catecholamines. The endogenous circadian rhythm has been implicated in the underlying mechanisms of a high incidence of cardiovascular events in morning hours. Thosar et al[73] performed a comprehensive circadian study of vascular endothelial function as assessed by brachial artery flow–mediated dilatation, showing that the endogenous circadian system affected the endothelial function in the vulnerable morning period associated with elevated plasma levels of malondialdehyde adducts (an oxidative stress marker) and endothelin-1 (a potent endothelium-derived vasoconstrictor peptide; Figure 2).

VASCULAR IMAGING

As reviewed by Nishimiya et al,[74] recent advances in vascular imaging have allowed us to capture the extent and characteristics of coronary plaques in vivo in more depth. In particular, more comprehensive quantitative assessments of coronary plaque composition, inflammation, and hemodynamic status, rather than conventional assessments of coronary luminal stenosis, have gained increasing attention.[75,76] Jarr et al[77] reported that 18F-fluorodeoxyglucose–positron emission tomography/computed tomography was useful for detecting vulnerable atherosclerotic plaques, as well as the response to therapeutic intervention in mice in vivo. Youn et al[78] showed the potential of ^{18}F-sodium fluoride–positron emission tomography/computed tomography to detect coronary plaques with high-risk features such as microcalcification and fibroatheromas. A recent study by Russo et al[79] demonstrated a high prevalence of healed culprit plaques in patients with stable angina pectoris in association with more advanced and vulnerable plaques even at nonculprit lesions, suggesting the panvascular nature

of coronary atherosclerosis. Nishiyama et al[80] visualized endothelial cell morphology such as endothelial pavementing in coronary arteries by means of a new form of optical coherence tomography with ultra-high resolution. This novel technology may provide insight into structural alterations of coronary arteries in patient with CMD.

EMERGING CLINICAL IMPLICATIONS OF CMD

Drug-Eluting Stent–Related Coronary Inflammation and Spasm

Although drug-eluting stents are currently the mainstay of PCI of significant coronary lesions, outstanding issues after stenting include neoatherosclerosis, coronary hyperconstricting responses (ie, coronary spasm), and inflammatory changes at the site of stent placement.[81,82] Coronary PVAT inflammation has been shown to be associated with enhanced coronary vasoconstrictive reactivity (Figure 1).[83,84] Harari et al[85] showed that everolimus-eluting stents caused endothelial barrier dysfunction and promoted neoatherosclerosis via interactions between canonical mTOR (mammalian target of rapamycin) inhibitors and the 12.6-kDa FKBP12 (FK506-binding protein 12). These alterations were mitigated by using a novel FKBP12-independent mTOR kinase inhibitor Torin-2–eluting stents.[85] We have recently demonstrated that drug-eluting stent–induced coronary hyperconstricting responses were exaggerated by the ligation of cardiac lymphatic vessels in association with more adventitial inflammation, more Rho kinase activation, and less adventitial lymphatic vessel formation in pigs in vivo.[86] This study suggests that cardiac lymphatic dysfunction may be a therapeutic target in the attempt to reduce coronary hyperconstricting responses induced by drug-eluting stents.[86]

Chronic Inflammatory Diseases

A chronic inflammatory milieu, which is commonly seen in patients with chronic inflammatory diseases, can affect coronary microvascular structure and function, leading to the development of CMD (Figure 1).[87] Inflammatory endothelial activation and oxidative stress play a potential mechanistic role linking chronic inflammatory rheumatoid diseases with CMD.[17] For example, psoriasis is a common chronic inflammatory skin disease, characterized by systemic inflammation affecting multiple organs in the body, including the coronary microvasculature (Figure 1).[88] A non-negligible prevalence of CMD has been reported in patients with psoriasis even in the absence of conventional coronary risk factors or overt CAD.[88] Using a deep sequencing omics approach, Garshick et al[89] revealed that circulating inflammasome signaling pathways, such as interleukins-1β and 6, were correlated with inflammatory endothelial activation markers in patients with psoriasis as compared with age- and sex-matched controls. Moreover, the same group also showed that in patients with psoriasis, platelets were activated to induce endothelial cell inflammatory responses via cyclooxygenase-1, which was improved by 2-week treatment with low-dose aspirin.[90] Furthermore, treatment with tumor necrosis factor (a proinflammatory cytokine) inhibitors in patients with psoriasis markedly improved coronary microvascular function as assessed by coronary flow reserve along with the reduction in systemic inflammatory biomarkers.[91] These results further support the role of inflammation in the pathophysiology of endothelial dysfunction and the increased risk of cardiovascular disease in patients with the disorder.[32] Potential strategies to attenuate vascular inflammation include targeting cholesterol metabolism, fatty acid mediators, and the autophagy-lysosome pathway.[92]

Coronavirus Disease 2019

An initial case series of coronavirus disease 2019 (COVID-19) patients with ST-segment elevation reported that 3 of 9 (33%) patients who underwent coronary angiography did not have obstructive CAD, raising the possibility that myocardial injury in these patients could be attributed, in part, to coronary functional abnormalities including CMD.[93] Preexisting endothelial dysfunction may predispose the patient to cardiovascular complications of COVID-19, such as cardiac dysfunction, myocarditis, and thromboembolism.[94,95] Briefly, it is speculated that the culprit virus severe acute respiratory syndrome coronavirus 2 binds and enters endothelial cells through ACE2 (angiotensin-converting enzyme 2).[94,95] The viral entry leads to degradation of ACE2, and the resultant loss of its activity contributes to cardiac dysfunction, coronary vasoconstriction, epicardial adipose tissue inflammation, and possibly coronary microcirculatory dysfunction.[94–96] However, it remains to be fully elucidated whether severe acute respiratory syndrome coronavirus 2 enters endothelial cells and ACE2 plays a role in this process. Sakamoto et al[97] confirmed that the expression of ACE2 was markedly reduced in postmortem COVID-19 hearts. In this study, ACE2 was scarcely detectable in the endothelium or pericytes of intramyocardial microvessels, but readily detectable in the endothelium of coronary arteries, implicating the viral involvement of coronary microvasculature.[97] Nagashima et al[98] found elevated endothelial expression of interleukin-6, tumor necrosis factor-α, intercellular adhesion molecule 1, and caspase-1 in postmortem lung samples from COVID-19 patients, providing evidence of endotheliopathy—a putative contributor to COVID-19–associated coagulopathy. Although no studies to date have directly addressed the role of angiotensin-(1–7) as a modulator of CMD, it is a potent vasodilator derived from angiotensin II by ACE2[22] and augments both NO- and EDH-mediated relaxations

in porcine coronary arteries.[99] Available evidence suggests that preserving ACE2 activity in the endothelium while preventing ACE2 cleavage to form soluble ACE2 may help to avoid unrestrained inflammatory responses associated with COVID-19 and thus may be beneficial for cardiovascular complications during the infection.[100] Many clinical trials are ongoing across the world to investigate the efficacy and safety of renin-angiotensin-aldosterone system modulators in the prevention and treatment of COVID-19.[100]

POTENTIAL THERAPEUTIC INTERVENTIONS

Statins

JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) showed that rosuvastatin significantly reduced the incidence of major cardiovascular events and death from any cause in apparently healthy people who had low-grade inflammation (a high-sensitivity C-reactive protein level of ≥0.2 mg/dL) but did not have hyperlipidemia (a low-density lipoprotein cholesterol level of <130 mg/dL).[101] In a primary prevention setting of the JUPITER population, Akintunde et al[102] showed that elevated levels of baseline group IIA secretory phospholipase A_2—an inflammatory mediator in the vasculature—were an independent predictor of incident cardiovascular events and that some single-nucleotide polymorphisms in *PLA2G2A* encoding the protein had a trend for higher risk of cardiovascular disease. A combination treatment with statins and angiotensin-converting enzyme inhibitors was effective for improving endothelial function and quality of life in patients with chest pain and normal coronary angiograms, possibly by reducing oxidative stress of the vascular wall.[103] The current European Society of Cardiology guidelines recommend statins in all patients with chronic coronary syndromes including CMD.[104] The ongoing WARRIOR trial (Women's Ischemia Trial to Reduce Events in Non-Obstructive CAD; NCT03417388) is a multicenter, prospective, randomized, blinded clinical trial (n=4422), testing the hypothesis that intense medical therapy of high-intensity statin, maximally tolerated angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, and aspirin will reduce major adverse cardiovascular events in female patients with symptoms and signs of ischemia but no obstructive CAD.[105] The study will be completed by December 30, 2022, and is expected to provide more definitive information on the management of patients with CMD.

Calcium Channel Blockers

Calcium channel blockers are the worldwide mainstay for treatment of coronary spasm at both epicardial and microvascular levels.[17] Interestingly, the extent of coronary perivascular inflammation was markedly decreased in the spastic coronary artery after treatment with calcium channel blockers.[84] In this study, benidipine was preferably used as the drug of choice for several reasons; benidipine is characterized by L-, N-, and T-type triple Ca channel blockade, high affinity for coronary artery smooth muscle cells, and more beneficial prognostic effects as compared with other major calcium channel blockers used for the treatment of vasospastic angina (eg, nifedipine, amlodipine, and diltiazem).[106] A recent study has demonstrated the advantage of T-type Ca channel blockade in suppressing vasospasm in small coronary arteries through EDH-mediated mechanisms.[107] These results shed light on the pleiotropic effects of benidipine on coronary inflammation and vasomotion abnormalities, although benidipine is available exclusively in several Asian countries (eg, Japan, China, Korea, and the Philippines) for the treatment of hypertension and vasospastic angina.[108]

Angiotensin-Converting Enzyme Inhibitors

A recent study showed that in hypertrophic cardiomyopathy patients with CMD, a 6-month treatment with an angiotensin-converting enzyme inhibitor perindopril at a dose of 10 mg/day improved myocardial blood flow only in the subset of patients without evidence of myocardial fibrosis assessed by magnetic resonance imaging.[109] Perindopril may be effective in improving CMD in the early stage of the disease.[109]

Endothelial Function-Guided Management

The ENDOFIND trial (Endothelial Function-Guided Management in Patients With Non-Obstructive Coronary Artery Disease)[110] is a currently ongoing large-scale randomized clinical trial to test the hypothesis that a peripheral endothelial function–guided early aggressive management, which consists of lifestyle management, optimal blood pressure, and glycemic control, and intensive use of statins and calcium channel blockers, can reduce the risk of major cardiovascular events in patients with nonobstructive CAD, in whom CMD is highly prevalent. The study intervention and follow-up will be completed before the end of December 2022.[110]

SUMMARY

As highlighted in this review, recent experimental and clinical studies that addressed broad issues in vascular biology and cardiovascular medicine have contributed to a better understanding of the pathophysiology and clinical implications of CMD from bench to bedside. Although much remains to be elucidated regarding the mechanism, management, treatment, and prevention of CMD, recent advances in the field will pave the way for

the development of novel therapeutic strategies targeting CMD to improve the clinical outcomes of patients with the disorder.

ARTICLE INFORMATION

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Affiliations

Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan (S.G., A.S., J.T., S.Y., H.S.). International University of Health and Welfare, Narita, Japan (H.S.).

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Disclosures

None.

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