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Endothelium in Coronary Macro- and Microvascular Diseases

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Abstract

The endothelium plays a pivotal role in the regulation of vascular tone by synthesizing and liberating endothelium-derived relaxing factors inclusive of vasodilator prostaglandins (e.g. prostacyclin), nitric oxide (NO), and endothelium-dependent hyperpolarization (EDH) factors in a distinct blood vessel-size dependent manner. Large conduit arteries are predominantly regulated by NO and small resistance arteries by EDH factors. Accumulating evidence over the past few decades has demonstrated that endothelial dysfunction and coronary vasomotion abnormalities play crucial roles in the pathogenesis of various cardiovascular diseases. Structural and functional alterations of the coronary microvasculature have been coined as coronary microvascular dysfunction (CMD), which is highly prevalent and associated with adverse clinical outcomes in many clinical settings. The major mechanisms of coronary vasomotion abnormalities include enhanced coronary vasoconstrictive reactivity at epicardial and microvascular levels, impaired endothelium-dependent and -independent coronary

vasodilator capacities, and elevated coronary microvascular resistance caused by structural factors. Recent experimental and clinical research has highlighted CMD as the systemic small artery disease beyond the heart, emerging modulators of vascular functions, novel insight into the pathogenesis of cardiovascular diseases associated with CMD, and potential therapeutic interventions to CMD with major clinical implications. Herein, we will summarize the current knowledge on the endothelial modulation of vascular tone as well as the pathogenesis of coronary macro- and microvascular diseases from bench to bedside, with a special emphasis placed on the mechanisms and clinical implications of CMD.

(229/250 words)

Key words: coronary artery disease, coronary microvascular dysfunction, endothelial function, endothelium, nitric oxide, vasospastic angina (6/3–6 key words or phrases)

Abbreviations

ACE: angiotensin-converting enzyme

CABG: coronary artery bypass grafting

CAD: coronary artery disease

CCB(s): calcium channel blocker(s)

CMD: coronary microvascular dysfunction

CO: carbon monoxide

DES: drug-eluting stents

EDH: endothelium-dependent hyperpolarization

EDCF(s): endothelium-derived contracing factor(s)

EDRF(s): endothelium-derived relaxing factor(s)

FMD: flow-mediated dilatation

HFpEF: heart failure with preserved ejection fraction

H_2O_2: hydrogen peroxide

H_2S: hydrogen sulfide

INOCA: ischemia and no obstructive CAD

MACE: major adverse cardiovascular events

NO: nitric oxide

PCI: percutaneous coronary intervention

PVAT: perivascular adipose tissue

RHI: reactive hyperemia index

VSA: vasospastic angina

VSMC: vascular smooth muscle cells

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Summary

Introduction

A mountain of evidence has accumulated over the past few decades demonstrating that endothelial dysfunction and coronary vasomotion abnormalities play essential roles in the pathogenesis of various cardiovascular diseases.[1,2] The major mechanisms of coronary vasomotion abnormalities include enhanced coronary vasoconstrictive reactivity at epicardial and microvascular levels, impaired endothelium-dependent and -independent coronary vasodilator capacities, and enhanced coronary microvascular resistance caused by structural factors (**Figure 1**).[3,4] The role of endothelial dysfunction has been well recognized in the

development and progression of coronary macro- and microvascular diseases, although Rho-kinase-induced myosin light chain phosphorylation with resultant hypercontraction of vascular smooth muscle cells (VSMC) rather than endothelial dysfunction[1] is the central mechanism of coronary artery spasm at epicardial[5,6] as well as at microvascular levels.[7] For better or for worse, previous studies exclusively focused on structural and functional abnormalities of "epicardial" coronary arteries (i.e. coronary macrovascular disease) in patients with coronary artery disease (CAD) because they are immediately visible on coronary angiography in the catheter laboratory and amenable to procedural approaches represented by percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). However, a nationwide large-scale cohort study in the United States assessing a total of 12,062,081 coronary revascularizations in patients with CAD revealed that risk-adjusted mortality significantly decreased after CABG but not after PCI regardless of clinical indications.[8] Thus, structural and functional abnormalities of the coronary microvasculature, which is referred to as coronary microvascular dysfunction (CMD), have gained growing attention as potential research and therapeutic targets in many clinical settings, including ischemic heart disease,[9-16] heart failure with preserved ejection fraction (HFpEF),[17-26] aortic stenosis,[27] and even non-cardiac diseases, such as chronic inflammatory disorders[28-32] and liver diseases.[33] The term "ischemia and no obstructive CAD (INOCA)" has been coined for patients who have chest pain regardless of the presence or absence of

coronary macrovascular disease (i.e. epicardial obstructive CAD).[34] Many studies have consistently revealed high prevalence and significant prognostic impact of CMD in patients with INOCA in both genders, especially in females.[9-16] Moreover, different subtypes of coronary vasomotion abnormalities often coexist in various combinations in a subclinical, asymptomatic manner even in the absence of obstructive CAD, causing myocardial ischemia due to CMD.[13,35-37] Indeed, the counterintuitive results of the two landmark clinical trials addressing the management of stable CAD, the Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina (ORBITA) Trial[38] and the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) Trial,[39] have questioned the benefit of PCI or CABG and have suggested the importance of the coronary microvascular physiology, which interventional strategy could not improve. Although these trials did not directly focus on coronary microvascular function, an intriguing speculation is that CMD, which is highly prevalent in patients with a wide spectrum of CAD, might have contributed to residual cardiac ischemia even after the successful coronary revascularization.

The endothelium plays a pivotal role in the regulation of vascular tone by synthesizing and liberating endothelium-derived relaxing factors (EDRFs), including vasodilator prostaglandins (e.g. prostacyclin), nitric oxide (NO), and endothelium-dependent hyperpolarization (EDH) factors, as well as endothelium-derived contracting factors

(EDCFs).[1,2] Endothelial dysfunction can be attributed to reduced production or action of EDRFs or increased responses of EDCFs, initiating the step toward atherosclerotic cardiovascular diseases.[2] In this review, we will summarize the current knowledge on the role of the endothelium in the regulation and modulation of vascular tone involved in the pathogenesis of coronary macro- and microvascular diseases from bench to bedside, with a special emphasis on the mechanisms and clinical implications of CMD.

Endothelial Modulation of Vascular Tone: Blood Vessel Size-Dependent Contribution of Endothelium-Derived Relaxing Factors

Figure 2 shows the key players of endothelium-dependent vasodilatation. Shear stress and various agonists stimulate endothelial cells to synthesize and release different EDRFs to cause relaxation of the underlying VSMC and subsequent vasodilatation.[1,2] To date, three kinds of EDRFs have been identified, including vasodilator prostaglandins, NO, and EDH factors.[1,2] EDH-mediated relaxations are observed in the presence of cyclooxygenase and NO synthase inhibitors and are associated with hyperpolarization of the neighboring VSMC.[40,41] The nature of EDH factors appears to be heterogeneous depending on species and vascular beds of interest,[42] including epoxyeicosatrienoic acids (metabolites of arachidonic P450 epoxygenase pathway),[43,44] electrical communication through gap junctions,[45] K^+ ions,[46] hydrogen sulfide (H_2S),[47,48] carbon monoxide (CO),[49] and as we have

identified, endothelium-derived hydrogen peroxide (H_2O_2).[50] Among them, EETs mainly take part in EDH-mediated relaxations in human,[51] canine,[52] porcine,[53] and bovine coronary arteries,[54] K^+ ions in porcine[55] and bovine[56] coronary arteries, CO in rat coronary arteries,[49] and endothelium-derived H_2O_2 at physiological low concentrations in the coronary circulation of humans[57,58] and animals.[59-63] Like other gaseous mediators, H_2S has pleiotropic cardiovascular effects, such as shear stress-mediated vasomotor control in coronary arteries,[64] arterial blood pressure-lowering effects,[65] and anti-inflammatory and anti-oxidant properties.[42] As illustrated in **Figure 2**, these EDRFs finely modulate vascular tone in a distinct blood vessel-size dependent manner; vasodilator prostaglandins play a small but invariable role, NO predominantly modulates the tone of large conduit arteries (e.g. epicardial coronary arteries) and the contribution of NO decreases as the blood vessel size decreases, whilst that of EDH increases as the blood vessel size decreases and consequently EDH-mediated responses are the major mechanism of vasodilatation in small resistance arteries (e.g. coronary microvessels).[1,66-68] This blood vessel size-dependent contribution of NO and EDH is well conserved across species from rodents to humans to achieve a physiological balance between them. Accordingly, EDH is especially important in microcirculations, where blood pressure and organ perfusion are mostly determined. It should be emphasized that epicardial coronary artery is just like a tip of the iceberg, because more than 95% of coronary vascular resistance is predominantly determined by the

pre-arterioles (more than 100 □m in diameter) and arterioles (less than 100 □m),[69] where EDH-mediated responses in the mechanism of vasodilatation become more important than NO-mediated relaxations. Multiple mechanisms are involved in the augmented EDH-mediated responses in small resistance arteries, including negative interactions between NO and several EDH factors.[68,70-74] Keeping these concepts in mind, in the treatment of patients with coronary macro- and microvascular diseases, cardiologists should pay more attention to microcirculations although they are invisible on routine coronary angiography. The reason for this will be discussed later.

Coronary Macrovascular Disease

Inflammation and Coronary Vasospastic Angina

Hypercontraction of VSMC mediated by Rho-kinase-induced myosin light chain phosphorylation rather than endothelial dysfunction is the predominant mechanism of coronary artery spasm.[1] Building on this mechanism, recent studies have revealed close relationships among inflammation, perivascular adipose tissue (PVAT), and vasa vasorum in the pathogenesis of coronary artery spasm. Briefly, a major inflammatory cytokine interleulin-1□ caused intimal thickening and coronary vasospastic responses to intracoronary serotonin or histamine via outside-to-inside signaling in pigs in vivo.[75] Multimodality imaging techniques, such as micro-computed tomography and optical frequency domain

imaging, enabled us to visualize enhanced adventitial vasa vasorum formation associated with coronary hyperconstriction via Rho-kinase activation in patients with VSA.[76,77] Vasa vasorum serves as a pipeline for inflammatory mediators derived from the surrounding inflamed adipose tissue to the local coronary atherosclerotic lesions in the vascular wall. Indeed, coronary vasoconstriction in response to intracoronary acetylcholine in patients with non-obstructive CAD was more prominent in coronary artery segments that had macrophage infiltration and vasa vasorum proliferation in an additive fashion than in those without both.[78] Inflamed PVAT plays important roles in the underlying mechanisms behind coronary vasomotion abnormalities. We have recently demonstrated that drug-eluting stent (DES) induced marked inflammation of coronary PVAT in association with coronary hyperconstricting responses in pigs in vivo[79] and that the extent of coronary perivascular inflammation in patients with VSA was markedly decreased in the spastic coronary artery in a reversible manner after a median treatment period of 23 months with calcium-channel blockers (CCBs),[80] the drug of choice for the treatment and prevention of coronary artery spasm.[81] Refer to concise reviews and our recent study for more information on the novel roles of PVAT and adventitial vasa vasorum in the modulation of vascular functions.[82-85]

Drug-Eluting Stent-Induced Coronary Inflammation and Spasm

Although DES is currently the mainstay of PCI to significant coronary lesions, unresolved

issues after coronary stenting include neoatherosclerosis, coronary hyperconstricting and inflammatory responses at the site of stent placement, and persistent or recurrent angina in the absence of residual epicardial stenosis.[86-89] Coronary PVAT inflammation following DES implantation[79,80] and cardiac lymphatic dysfunction[90] have been shown to be involved in enhanced coronary vasoconstrictive reactivity, suggesting that inflamed PVAT and cardiac lymphatic dysfunction may be novel therapeutic targets to reduce coronary hyperconstricting responses caused by DES.

Coronary Microvascular Disease

Mechanisms, Prevalence, and Clinical Significance of CMD

A growing body of experimental and clinical evidence has highlighted the crucial role of CMD in the pathophysiology of cardiac ischemia in patients with various cardiovascular diseases with major clinical implications.[4] The underlying mechanisms of CMD appear to be multifarious, including several structural and functional alterations; enhanced coronary vasoconstrictive reactivity (e.g. coronary spasm) at epicardial and microvascular levels, impaired endothelium-dependent and -independent coronary vasodilator capacities, and enhanced coronary microvascular resistance caused by structural factors (e.g. luminal narrowing, vascular remodeling, vascular rarefaction, and extramural compression), all of which can cause myocardial ischemia and often overlap and coexist in various combinations

even without the presence of obstructive CAD (**Figure 3**).[3,4,35,37,108] Coronary microvascular spasm is defined as reproduction of angina symptoms, ischemic ECG changes, but no epicardial spasm in response to intracoronary acetylcholine provocation testing.[91] The major mechanisms of coronary microvascular spasm include Rho-kinase-mediated myosin light chain phosphorylation,[7] increased production of vasoconstrictive mediators, such as serotonin,[92] endothelin-1,[93,94] and neuropeptide Y,[95] and inflammatory conditions in the coronary microvasculature[96] with resultant enhanced coronary vasoconstrictive reactivity. MicroRNAs are small non-coding RNAs regulating gene expressions via degradation or translational repression of mRNA and play various regulatory roles in the cardiovascular system.[97] For instance, microRNAs-125a/b-5p are highly expressed in vascular endothelial cells and inhibit the expression of endothelin-1.[98] A previous study showed decreased levels of microRNA 125a-5p in parallel with increased levels of plasma endothelin-1 in patients with takotsubo cardiomyopathy, giving support to the coronary microvascular spasm hypothesis of the disease.[99] Readers are encouraged to refer to the comprehensive review article on the contemporary experimental animal models of CMD with a keen insight into anatomical, metabolic, and mechanistic considerations of different models.[100]

The prevalence of CMD in patients with CAD has been shown to be unexpectedly high. Indeed, more than half of patients undergoing invasive coronary angiography for the evaluation of suspected coronary macrovascular disease have no significant coronary artery

stenosis.[101] A large cohort study (n=1,439) from Mayo Clinic showed that about two-thirds of patients with chest pain who had angiographically normal coronary arteries or non-obstructive CAD had either endothelium-dependent or -independent CMD, which was evaluated by invasive coronary reactivity testing.[13] This clinical entity has been referred to as INOCA, in which the role of CMD has been recognized as an alternative etiology of symptoms and signs of myocardial ischemia.[34] Moreover, recent studies comprehensively assessing coronary physiology by multimodality protocols revealed that a substantial proportion of patients with INOCA differ in the underlying coronary microvascular disease.[13,35,36,85] Furthermore, we have recently demonstrated, in patients with VSA, a significant 5% increased risk of major adverse cardiovascular events (MACE) for each 1-point increase in index of microcirculatory resistance (IMR), a catheter-derived measure of CMD.[37] If complicated with CMD, patients with INOCA are associated with increased future adverse cardiac events, including myocardial infarction, percutaneous or surgical revascularization, cardiac death, and hospitalization for unstable angina.[102-105] As extensively reviewed elsewhere[106,107] and summarized in **Table 1**, several methods are available for appraising coronary microvascular function, with variable differences in costs, invasiveness, accessibility, evaluable measures, and diagnostic accuracy. Although the diagnostic accuracy of contemporary non-invasive stress tests is limited for detecting CMD,[13,108] comprehensive invasive assessment of coronary vasomotor reactivity using

intracoronary acetylcholine, adenosine, and other vasoactive agents is feasible, safe, and of diagnostic value to extract patients with CMD.[13,35,109-113] Such structured approach to endotype patients with CMD based on the underlying mechanism of coronary vasomotion abnormalities may be important to tailor the most appropriate treatment and may provide physicians with useful information to assist decision making and risk stratification beyond conventional risk factors.

CMD as Systemic Vascular Disease beyond the Heart

Recent studies have revealed that coronary vasomotion abnormalities are often concomitant with peripheral endothelial dysfunction, where CMD is a cardiac manifestation of the systemic small artery disease.[114-118] We simultaneously examined endothelial functions of peripheral conduit and resistance arteries in patients with VSA and microvascular angina,[118] which were diagnosed by coronary spasm provocation testing using intracoronary acetylcholine.[91,119] The major finding was that bradykinin-induced endothelium-dependent vasodilatations in fingertip arterioles were almost absent in patients with microvascular angina.[118] Mechanistically, both NO- and EDH-mediated digital vasodilatations were markedly impaired in patients with microvascular angina, suggesting that CMD is a manifestation of systemic vascular dysfunction beyond the heart.[118]

Primary Coronary Microcirculatory Dysfunction and Vulnerable Patient

Endothelium-Dependent CMD and Advanced Coronary Atherosclerosis

We examined whether endothelium-dependent CMD is associated with coronary atherosclerosis in patients with INOCA.[120] Endothelium-dependent coronary vascular reactivity was evaluated with graded doses of intracoronary acetylcholine and endothelium-dependent CMD was defined as a percent increase in coronary blood flow of less than 50% in response to acetylcholine.[102,121-123] Patients with VSA, which was defined as transient total or subtotal coronary artery occlusion (more than 90% constriction) with chest pain and ischemic ECG changes in response to acetylcholine, were excluded because of a limitation of acetylcholine for testing endothelium-dependent CMD; acetylcholine is not a pure endothelium-dependent agonist but rather evokes VSMC-dependent vasoconstriction in patients with VSA who have enhanced coronary vasoconstrictive reactivity.[1,111] The major finding was that patients with endothelium-dependent CMD showed larger plaque burden and plaque volume in association with more vulnerable plaque characteristics as evaluated by virtual-histology intravascular ultrasound.[120] These patients showed larger necrotic core volume and higher frequency of thin-capped fibroatheroma, which is characteristic of rupture-prone vulnerable plaques.[120] These results are consistent with previous studies showing the association between endothelium-independent CMD and vulnerable plaque characteristics.[124-126]

Endothelium-Dependent CMD and Local Low Shear Stress

Shear stress is one of the important physiological stimuli that make endothelial cells synthesize and liberate EDRFs to maintain vascular homeostasis, whereas altered oscillatory or low shear stress with a disturbed flow pattern on coronary artery wall contributes to the local progression of atherosclerotic coronary plaque through endothelial and VSMC proliferation, inflammation, lipoprotein uptake, and leukocyte adhesion.[127,128] Indeed, previous studies have shown that altered shear stress on the coronary artery wall is associated with the local progression of atherosclerotic coronary plaque,[129] and that coronary endothelial shear stress decreases as changes in coronary blood flow in response to acetylcholine decrease.[123] Taken together, endothelium-dependent CMD is involved in coronary atherosclerosis progression, possibly via low endothelial shear stress.[130]

The Vulnerable Microcirculation Concept

The aforementioned lines of evidence support the concepts of "primary coronary microcirculatory dysfunction"[131] and "vulnerable patient".[132] Patients with chest pain but without angiographical abnormalities are often underdiagnosed and are offered no therapeutic intervention or follow-up under the umbrella of "normal" coronary arteries. On the contrary, patients with CMD may be predisposed to the development of more vulnerable coronary

atherosclerosis and therefore may be prone to future coronary events.[85]

Clinical and Therapeutic Considerations

Smoking and Vaping: A Modifiable Risk factor for Coronary Macro- and Microvascular Diseases

Among traditional risk factors for coronary atherosclerotic disease, cigarette smoking is well recognized as a major risk and prognostic factor for VSA,[133,134] and undoubtedly smoking cessation is the mainstay of symptomatic and prognostic improvement in patients with VSA.[133] Mechanistically, superoxide anions derived from cigarette smoke extract can accelerate the oxidative degradation of NO, directly damage endothelial cells, and promote vascular inflammatory responses, leading to coronary hypercontraction.[135,136] Recently, the evolving use of vaping products has been implicated in the pathogenesis of macro- and microvascular diseases.[137-140] For example, mentholated cigarette smoking can reduce coronary flow reserve to the same extent as regular cigarettes.[137] Flavoring additives in electronic cigarettes can cause endothelial dysfunction by increasing vascular inflammatory responses as well as oxidative stress and thus by decreasing NO bioavailability.[138,139] Moreover, electronic cigarette smoking can elicit an acute vasoconstrictive response in the microvasculature, although an index of microvascular endothelial function, reactive hyperemia index paradoxically increases immediately after electronic cigarettes use.[140] The

Sapienza University of Rome-Vascular Assessment of Proatherosclerotic Effects of Smoking (SUR-VAPES) 3 Trial is designed to examine the acute effects of electronic vaping cigarettes and heat-not-burn cigarettes on coronary vasomotor function assessed by invasive coronary reactivity testing, including coronary flow reserve, fractional flow reserve, and instantaneous wave-free ratio.[141,142] The results of this trial will bring more detailed information on the effects of novel smoking products on the coronary macro- and microcirculation.[141,142]

Supplemental NO: Too Much of a Good Thing?

Since the discovery of the acute anti-anginal effect of nitroglycerin over 140 years ago by Murrell,[143] the use of nitrates as a NO donor has served as the most common treatment in the acute phase of ischemic heart disease and heart failure. As discussed above, the emerging role of CMD has been implicated in patients with various cardiovascular diseases, including obstructive CAD who underwent successful revascularization,[38] INOCA,[34] VSA,[37] and HFpEF.[17-19] Contrary to the premise that enhancing NO-mediated vasodilatation by means of supplemental NO could exert beneficial effects on these patients, the results of systemic and long-term administrations of nitrates were unexpectedly neutral or even harmful in patients with residual microvascular ischemia despite successful PCI,[144] myocardial infarction,[145] VSA,[146] and HFpEF.[147,148] These lines of evidence suggest the potential harms of NO therapy and the need to turn our attention to avoid excessive NO supplementation. A

possible explanation for such a “paradox” of NO-targeted therapy may be nitrosative stress caused by an excessive amount of supplemental NO.[149,150] Moreover, in light of the facts that there are significant negative interactions between NO and several EDH factors[68,70-73] and that coronary vascular resistance is predominantly determined by the coronary microcirculation,[69] where the effect of EDH-mediated responses on vascular tone overwhelms that of NO-mediated relaxations, it is important to consider the blood vessel size-dependent contribution of NO and EDH factors in the treatment of CMD. Actually, intracoronary administration of nitroglycerin does not increase coronary blood flow.[120] Taken together, based on the underlying mechanism of coronary vasomotion abnormalities, identifying the specific indications and contraindications of chronic NO supplementation may be important to tailor the most appropriate treatment; a good example of this approach is available elsewhere.[110,151,152]

Clinical Trials Targeting Endothelial Function and Coronary Microvascular Function

The assessment of endothelial function in the clinical settings has been accepted as an excellent surrogate marker of cardiovascular risk.[153] For instance, impaired flow-mediated dilatation (FMD) of the brachial artery and digital reactive hyperemia index (RHI) in peripheral arterial tonometry are both associated with future adverse cardiovascular events in patients with CAD,[154-156] and one standard deviation reduction in FMD or RHI is associated

with doubling of adverse cardiovascular event risk.[157] FMD and RHI reflect peripheral macro- and microvascular endothelial function, respectively, however, both indices are often impaired in patients with CMD,[158,159] again suggesting the systemic nature of the disorder.

The current European Society of Cardiology guidelines recommend the use of statins in all patients with chronic coronary syndromes including CMD.[160] The guidelines also suggest treatment with □-blockers, angiotensin-converting enzyme (ACE) inhibitors, and statins for patients with reduced coronary flow reserve or increased IMR and a negative acetylcholine provocation test, which are suggestive of impaired coronary vasodilator capacities, while CCBs and long-acting nitrates for patients with coronary microvascular spasm.[160] Previous animal studies demonstrated that ACE inhibitors are capable of potentiating endothelium-dependent relaxations mediated by both NO and EDH factors in the coronary circulation.[161,162]

Based on the premise that a tailored therapeutic strategy,[110] such as a stratified medical treatment driven by the results of coronary reactivity testing and endothelial function-guided management, may be beneficial in patients with CMD, several clinical trials have been launched. For example, a multicenter, prospective, randomized, blinded clinical trial, the Women's Ischemia Trial to Reduce Events in Non-Obstructive CAD (WARRIOR) Trial (NCT03417388) (n=4,422) is ongoing to test the hypothesis that intensive medical treatment consisting of high-intensity statins, maximally tolerated doses of ACE

inhibitors/angiotensin receptor blockers, and aspirin would reduce the risk of MACE in female patients with symptoms and/or signs of myocardial ischemia but no obstructive CAD.[163] Another large-scale randomized clinical trial, the Endothelial Function-Guided Management in Patients with Non-obstructive Coronary Artery Disease (ENDOFIND) Trial is currently ongoing to address whether an peripheral endothelial function-guided early aggressive management, which consists of lifestyle management, optimal blood pressure, and glycemic control, and the intensive use of statins and CCBs, could reduce the risk of MACE in patients with non-obstructive CAD, in whom CMD is highly prevalent.[164] Both trials will be completed by the end of 2022 and are expected to provide informative evidence on the management of patients with CMD. Additionally, the Ticagrelor and Preconditioning in Patients with Coronary artery disease (TAPER-S) Trial aims to assess the pleiotropic effects of a reversibly binding, direct-acting, oral, P_2Y_{12} antagonist ticagrelor on ischemic preconditioning and coronary microvascular function in patients with stable multivessel CAD undergoing staged, fractional flow reserve-guided PCI.[165] This trial has been completed by November 2020 and the results are awaited with interest.

Summary

This review highlights the evolving landscape of coronary vasomotion abnormalities in general and endothelium-related CMD in particular (**Table 2**). Patients with coronary

vasomotion abnormalities are often complicated with inflammatory responses and peripheral endothelial dysfunction, in which CMD manifests as systemic vascular dysfunction beyond the heart. Novel therapies to improve CMD may attenuate the progression of coronary atherosclerosis and early aggressive medical management upon detection of CMD may benefit the vulnerable patients. In an attempt to optimize the treatment, consideration of CMD should not be lost even in the presence of normal coronary angiogram. Rather, given the high prevalence and adverse clinical impact of CMD, consideration of coronary microvascular function should be implemented in both basic research and clinical practice for the purpose of improving health care and outcomes of patients with the disease.

In conclusion, further characterization and better understanding of the roles of the endothelium in the pathophysiology and clinical outcomes of coronary macro- and microvascular diseases can be an important gateway to this end.

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Figure legends

Figure 1. Mechanisms of Coronary Macro- and Microvascular Dysfunction.

Figure 2. Blood Vessel-size Dependent Endothelial Modulation of Vascular Tone and Rho-Kinase-Mediated Hypercontraction of Vascular Smooth Muscle.

EDH, endothelium-dependent hyperpolarization; NO, nitric oxide.

Figure 3. Overlap and Coexistence of Coronary Macro- and Microvascular Dysfunctions.

Each number corresponds to the reference.

Tables

Table 1. Invasive and non-invasive methods for appraising coronary microvascular function

Methods	Measures	Features
Invasive		
CAG review	TIMI frame count	Easily obtainable but semi-quantitative
Coronary reactivity testing		Enables endotyping of CMD
ACh/EM	Coronary spasm	Established as provocative spasm testing
CS sampling during ACh/EM	Lactate production rate	Enables the accurate diagnosis of MVS
Doppler flow/temperature wire	ACh-induced CBF	Endothelium-dependent responses
	ATP-induced CFR	Endothelium-independent responses
Pressure-thermodilution wire	IMR	Reflects pure microvascular function
Non-invasive		During endothelium-independent maximum hyperemia
Doppler echo	CFR	Readily available but operator-dependent
CMR	CFR	The most reliable non-invasive method
PET	CFR	The most reliable non-invasive method

ACh: acetylcholine; ATP: adenosine triphosphate; CAG: coronary angiography; CBF: coronary blood flow; CFR: coronary flow reserve; CMD: coronary microvascular dysfunction; CMR: cardiac magnetic resonance; echo: echocardiography; CS: coronary sinus; EM: ergometrine (ergonovine); IMR: index of microvascular resistance; MVS: microvascular spasm; PET: positron emission tomography.

Table 2. Summary and perspective

Highlights
1. Endothelial dysfunction and coronary macro- and microvascular dysfunction play crucial roles in the pathogenesis of various cardiovascular diseases.
2. The endothelium modulates vascular tone in a vessel-size dependent manner: A) Large conduit arteries are predominantly regulated by NO B) Small resistance arteries by EDH factors
3. The major mechanisms of coronary vasomotion abnormalities are threefold: A) Enhanced coronary vasoconstrictive reactivity at epicardial and microvascular levels B) Impaired endothelium-dependent and -independent coronary vasodilator capacities C) Elevated coronary microvascular resistance caused by structural factors
4. Given the high prevalence and adverse clinical impact of CMD, consideration of and novel therapies for CMD appear to be important for vulnerable patients.

CMD: coronary microvascular dysfunction; EDH: endothelium-dependent hyperpolarization; NO: nitric oxide.

Figure 1

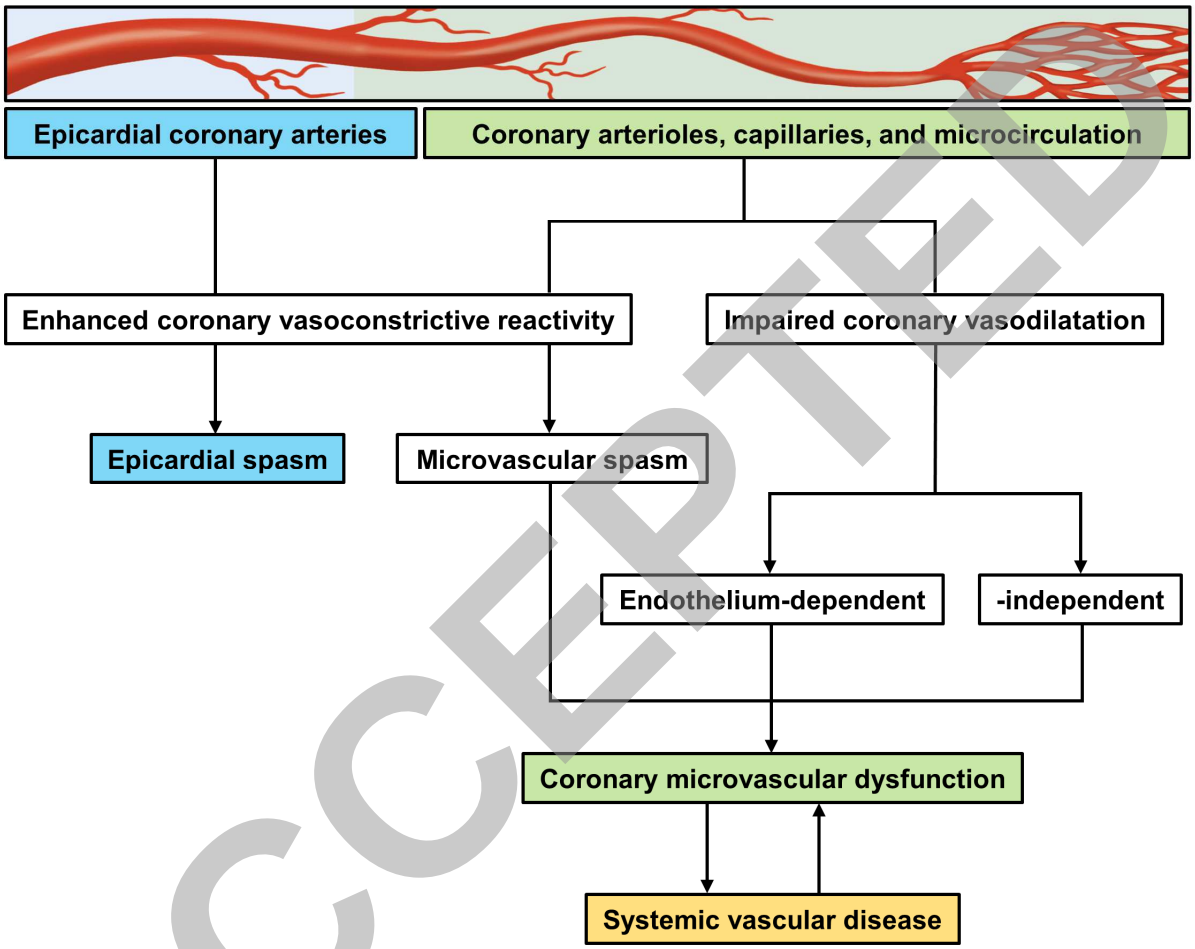

Figure 1. Mechanisms of Coronary Macro- and Microvascular Dysfunction.

Figure 2

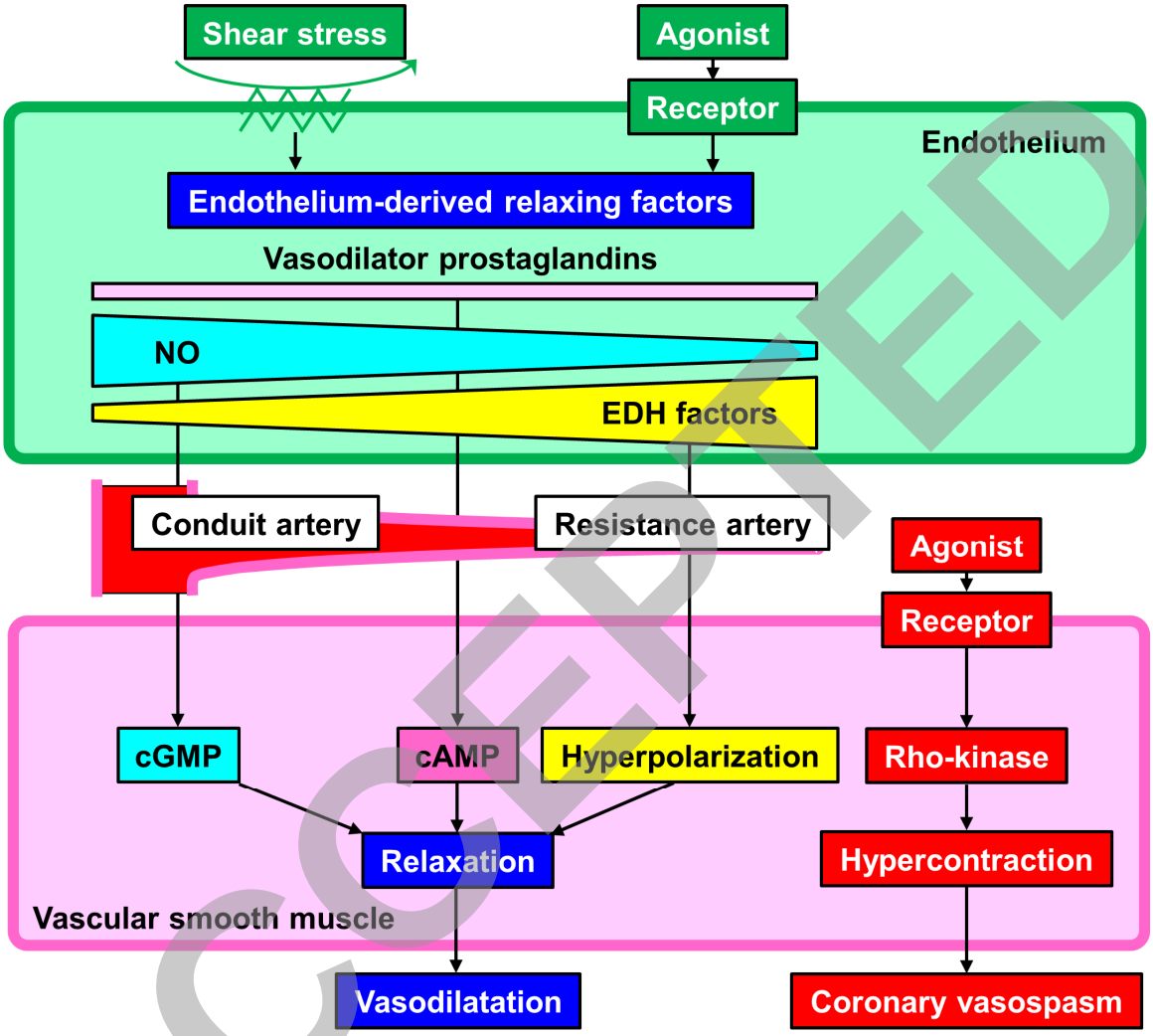

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Figure 3

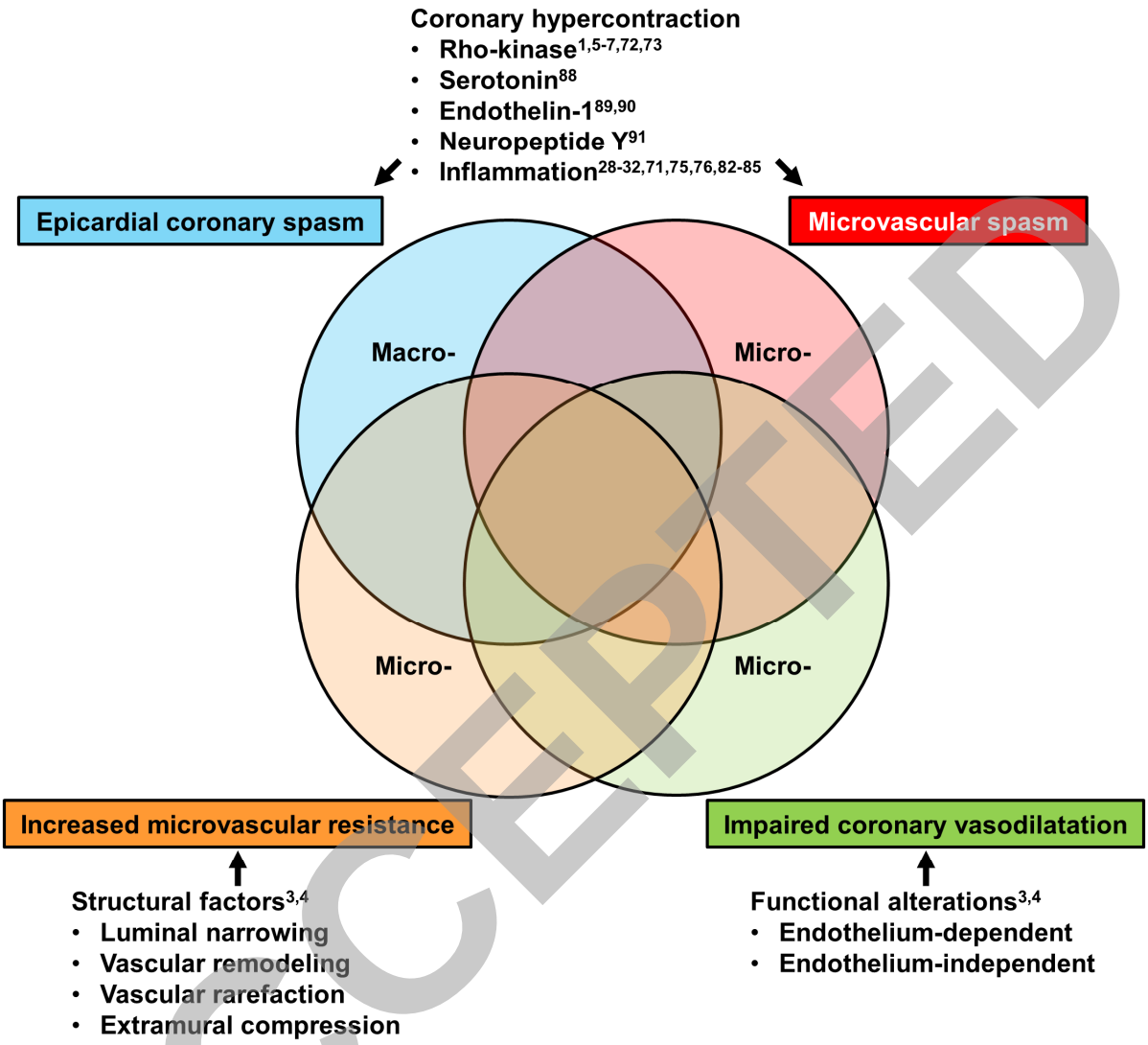

Figure 3. Overlap and Coexistence of Coronary Macro- and Microvascular Dysfunctions.
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