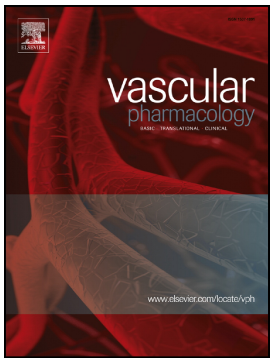

Roles of endothelial and smooth muscle cell dysfunction and vasa vasorum in vasomotor disorders in ischemia with no obstructive coronary artery disease

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Title: **Roles of endothelial and smooth muscle cell dysfunction and vasa vasorum in vasomotor disorders in ischemia with no obstructive coronary artery disease**

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Abstract

Recently, the importance has emerged of ischemia with no obstructive coronary artery disease (INOCA), for which endothelial and vascular smooth muscle cell (VSMC) dysfunctions and alterations in coronary vasa vasorum are involved. Regarding endothelial vasodilator functions, both endothelium-derived nitric oxide and endothelium-derived hyperpolarizing factor play important roles in modulating vascular tone, especially in the microcirculation. Recent studies have suggested systemic endothelial dysfunction in INOCA. Regarding VSMC dysfunction, Rho-kinase has been identified as a key molecular mechanism of VSMC hyperconstriction in INOCA. Finally, recent advances of coronary imaging have demonstrated the important role of altered adventitial vasa vasorum functions in INOCA. (100/100 words)

Keywords: Ischemia with no obstructive coronary artery disease (INOCA); coronary microvascular dysfunction (CMD); endothelial cell; vascular smooth muscle cell; vasa vasorum.

Main Text

In the pathogenesis of chronic coronary syndrome (CCS), three mechanisms are known to be involved, alone or in combination, including atherosclerotic stenosis of epicardial coronary artery, vasospasm of epicardial coronary artery, and coronary microvascular dysfunction (CMD). The latter two mechanisms are collectively termed as ischemia with no obstructive coronary artery disease (INOCA) [1, 2]. In the pathogenesis of INOCA, endothelial and vascular smooth muscle cell (VSMC) dysfunctions are involved, alone or in combination [3]. Furthermore, alterations in the functions of coronary adventitial vasa vasorum also appear to be involved [3]. Recently, the importance of INOCA/CMD has emerged, as demonstrated by several important clinical studies, including the international COVADIS registry study [4], demonstrating that microvascular angina is not a benign disease but is associated with substantial cardiovascular events regardless of sex or ethnicity [4].

The endothelium plays an important role in modulating vascular tone by synthesizing and releasing endothelium-derived relaxing factors (EDRFs), including prostacyclin, nitric oxide (NO), and endothelium-derived hyperpolarizing factor (EDHF) [5]. The important point on EDRFs, especially when considering microcirculation, is that endothelium-derived NO plays a major role in large arteries, while the importance of EDHF increases as vessel size decreases [6, 7]. We identified that one of the major candidates for EDHF is hydrogen peroxide (H_2O_2) released by the endothelium at physiological concentrations [8]. Endothelial NO synthase generates superoxide anion even under physiological condition, which is metabolized to H_2O_2 by Cu,Zn-superoxide dismutase (SOD) and rapidly diffuses to the underlying VSMC, causing vasodilatation through opening Ca^{2+}-activated K channels [8]. We then demonstrated that EDHF/H_2O_2 plays an important protective role against nitro-stress caused by excessive NO, and that the physiological balance between NO and EDHF/H_2O_2 plays an important role for the maintenance of cardiovascular homeostasis [9]. Importantly, when we measured endothelial vasodilator functions in the forearm circulation of patients with microvascular angina, while NO-mediated dilatation of brachial artery was fairly preserved, endothelium-dependent vasodilatation of finger-tip microvessels were markedly reduced, suggesting that microvascular angina is a cardiac manifestation of systemic endothelial dysfunctions (NO/EDHF) [10] (**Figure**).

We and others repeatedly demonstrated that VSMC hyperconstriction, but not endothelial dysfunction, plays a major role for coronary artery spasm [3, 7]. Rho-kinase, which is a

downstream molecule of the small G-protein RhoA, plays an important role as a molecular switch for VSMC contraction through inhibition of myosin phosphatase. We identified that upregulated Rho-kinase plays a key role in the molecular mechanisms of coronary artery spasm in animal models of spasm and in patients with vasospastic angina (VSA), and that Rho-kinase activation is substantially involved in the pathogenesis of atherosclerosis in general [7]. We further demonstrated that fasudil, which is used for the treatment of cerebral vasospasm after cerebral hemorrhage in Japan, is metabolized to hydroxyfasudil, exerting its specific and potent inhibitory effects on Rho-kinase [7]. Interestingly, although fasudil suppressed epicardial coronary spasm in almost all patients with VSA [11], it inhibited coronary microvascular spasm in two thirds of patients with microvascular angina, suggesting heterogeneity in the pathogenesis of the disorder [12]. Importantly, when epicardial coronary spasm and MVD coexist in patients with INOCA, the long-term prognosis is worse compared with each of them, and that Rho-kinase activation is involved in both of them [13] (**Figure**).

Recent advances in intracoronary imaging have enabled us to visualize vasa vasorum in the coronary adventitia in patients with INOCA. Indeed, using optical frequency domain imaging (OFDI) technique, we were able to demonstrate that adventitial vasa vasorum density is enhanced at the spastic coronary segment of patients with VSA [14]. We divided the patients with suspected INOCA into 4 groups, including control, microvascular spasm, diffuse epicardial coronary spasm, and focal epicardial coronary spasm, and examined them with optical coherence tomography (OCT) imaging [14]. We found that microvascular spasm develops first, followed by diffuse/focal coronary spasm, where the long-term prognosis is worst in the focal spasm group with the highest prevalence of unstable intraplaque neovessels [15]. Using FDG-PET, we could also demonstrate that coronary adventitial inflammation is present at the spastic coronary segment in the acute phase, and that this disappeared after long-term medical treatment associated with improved symptoms in the chronic phase, demonstrating the importance of coronary adventitial inflammation in the pathogenesis of coronary spasm [3, 7] (**Figure**). This notion is supported by our previous finding that chronic adventitial inflammation causes enhanced coronary vasospastic responses in pigs in vivo [3].

In summary, the importance of coronary functional abnormalities has emerged in the pathogenesis of CCS, for which both endothelial and VSMC dysfunctions play important roles, and with alterations in the adventitial vasa vasorum in epicardial coronary arteries also being apparently involved [3, 7] (**Figure**). Thus, new treatment of INOCA should focus on how to improve endothelial and VSMC dysfunctions and alterations in the adventitial vasa vasorum.

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Figure legend

Coronary functional abnormalities, including endothelial and smooth muscle cell dysfunctions, play important role in the pathogenesis of myocardial ischemia. For endothelial vasodilator function, endothelium-derived NO plays a major role in large arteries, while the importance of EDHF increases as vessel size decreases. For VSMC dysfunction, Rho-kinase plays an important role for

VSMC hypercontraction. In addition, alterations in coronary adventitial vasa vasorum are involved in VSMC dysfunction and plaque instabilization.

Re: VPH-D-23-00238/R1 (Author statement)

Dear Dr. Miano:

As a single author of this manuscript, I played all the roles to prepare the manuscript.

Thank you.

Sincerely yours,

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Conflict of Interest

I have no conflict of interest to disclose regarding my manuscript.

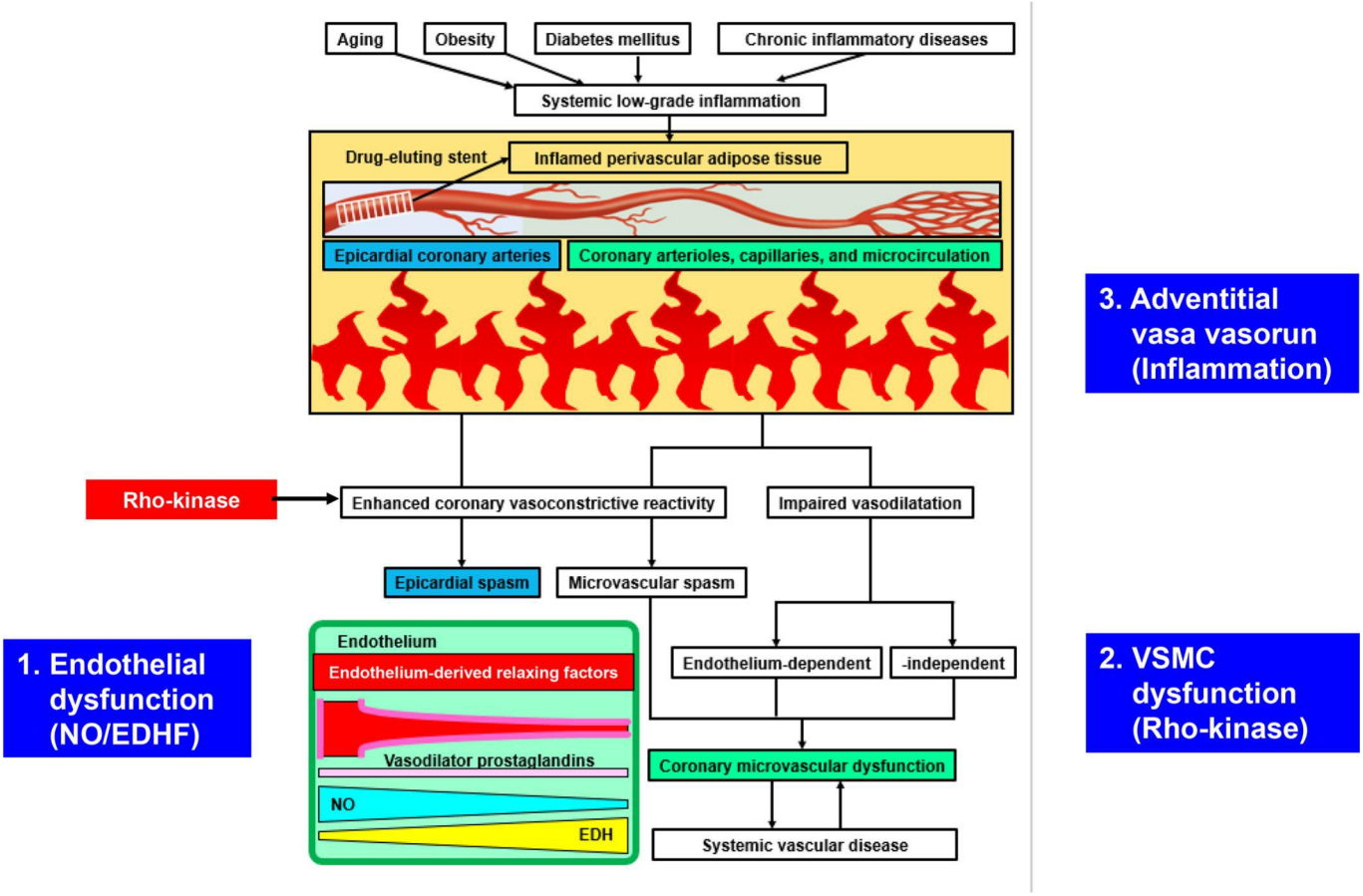
Aging
Obesity
Diabetes mellitus
Chronic inflammatory diseases
Systemic low-grade inflammation
Drug-eluting stent
Inflamed perivascular adipose tissue
Epicardial coronary arteries
Coronary arterioles, capillaries, and microcirculation
3. Adventitial vasa vasorun (Inflammation)
Rho-kinase
Enhanced coronary vasoconstrictive reactivity
Impaired vasodilatation
Epicardial spasm
Microvascular spasm
1. Endothelial dysfunction (NO/EDHF)
Endothelium
Endothelium-derived relaxing factors
Vasodilator prostaglandins
NO
EDH
Endothelium-dependent
-independent
2. VSMC dysfunction (Rho-kinase)
Coronary microvascular dysfunction
Systemic vascular disease

Figure 1