Review

The role of vascular failure in coronary artery spasm

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KEYWORDS
Coronary spasm; Endothelium; Vascular smooth muscle; Vascular failure

Summary
Coronary artery spasm plays an important role in the pathogenesis of angina pectoris as well as acute coronary syndrome and sudden death. The prevalence of coronary spasm is greater in East Asian populations than in other parts of the world. Although the mechanism of coronary spasm is still unclear, both endothelial and smooth muscle dysfunction have been reported to play a role. We recently proposed a new concept termed 'vascular failure' that represents an integration of endothelial and smooth muscle abnormalities. Thus, vascular failure is the primary cause of coronary artery spasm.

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Introduction

Angina pectoris is a clinical syndrome caused by transient myocardial ischemia due to an imbalance between the myocardial oxygen supply and demand. Classical or exertional angina is characterized by the following features: (I) the attack is induced by exertion and relieved by rest or nitroglycerin administration; and (II) the attack is associated with ST-segment depression on the electrocardiogram.

Coronary spasm plays an important role in angina pectoris as well as acute coronary syndrome [1]. Coronary spasm is defined as abnormal contraction of an epicardial coronary artery resulting in myocardial ischemia (Fig. 1). The manifestations commonly associated with myocardial ischemia are chest discomfort and ST elevation or depression on the electrocardiogram. ST elevation denotes transmural myocardial ischemia, whereas ST depression indicates nontransmural or subendocardial ischemia. The most sensitive marker of myocardial ischemia is the appearance of a wall motion abnormality, which can be detected by echocardiography.
The role of vascular failure in coronary artery spasm

The production of lactate is a metabolic marker of myocardial ischemia [3].

To evaluate the incidence of coronary spasm in Japanese patients with angina pectoris, we investigated 2195 patients with angina who were consecutively admitted to one of the major institutes in Japan from 1998 to 1999 (mean age, 65.2 years). Of the 2195 patients with angina, 921 (42%) had coronary spasm. The number of patients with angina pectoris increases with an increase in age. The mean age of the patients with coronary spasm was 62.5 ± 10.3,
Age distribution of coronary spastic angina and stable effort angina in Japanese patients with angina pectoris.

whereas that of the patients with stable effort angina was 67.0 ± 9.2 (p < 0.01). The age distribution was relatively younger in the patients with coronary spasm than in those with stable effort angina (Figs. 2 and 3). The prevalence of hypertension, diabetes mellitus, and low high-density lipoprotein (HDL)-cholesterol was lower in the patients with coronary spasm than in those with stable effort angina (hypertension, 39.8% vs. 49.0%; diabetes, 12.4% vs. 23.2%; low HDL cholesterol, 16.6% vs. 30.6%; p < 0.01). In contrast, the proportion of smokers was higher in the patients with coronary spasm than in the patients with stable effort angina (42.6% vs. 32.6%, p < 0.01). Most of the patients with coronary spasm did not have significant fixed coronary stenosis, whereas all patients with stable effort angina had significant fixed coronary stenosis (Table 1).

Vascular failure

Atherosclerosis is a progressive disease characterized by the response of the vessel wall to chronic, multifactorial injury that ultimately leads to the formation of atheromatous or fibrous plaques. We recently proposed a new concept termed 'vascular failure' that represents an integration of the endothelial and smooth muscle abnormalities [4] (Fig. 4).

It is now well recognized that endothelial dysfunction is the initial stage of atherosclerosis. Endothelial dysfunction is characterized by an impairment of the balance between endothelium-derived relaxing factors and endothelium-derived constricting factors [5,6]. Thus, endothelial dysfunction is not only the initial stage of atherosclerosis but also plays a key role in angina pectoris induced by coronary spasm.

Endothelial function in coronary spasm

The endothelium is a flat monolayer of cells that covers the vascular lumen throughout the human body. Endothelial cells are not merely constituents of the vessel wall, but play important roles in several biological processes [7]. Thus, the vascular endothelium has been characterized as a multifunctional organ that is essential to normal vascular physiology and plays a critical role in the pathogenesis of vascular disease. In fact, there are several studies that show that endothelial dysfunction is an independent predictor of cardiovascular events [8—10]. The presence of endothelial dysfunction is an essential component of vascular failure.

Acetylcholine causes vasodilation by releasing nitric oxide or closely-related substances [5,6]. Coronary spasm can be induced by methacholine or acetylcholine in patients with coronary spasm via muscarinic receptors [11,12] (Table 2). In humans, acetylcholine, serotonin, histamine, and ergonovine are all endothelium-dependent vasodilators, since they release nitric oxide and induce coronary dilation in young healthy subjects; however, they cause vasoconstriction in patients with atherosclerosis [6,13—15]. Thus, patients with coronary spasm have a disturbance in endothelial function of the coronary arteries [16].

### Table 1: Characteristics of patients with coronary spasm or stable effort angina.

<table>
<thead>
<tr>
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<th>Coronary spasm (n = 921)</th>
<th>Stable effort angina (n = 1274)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>62.5 ± 10.3</td>
<td>67.0 ± 9.2</td>
</tr>
<tr>
<td>Sex (men)</td>
<td>607(65.9%)</td>
<td>896(70.3%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>367(39.8%)</td>
<td>624(49.0%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>114(12.4%)</td>
<td>296(23.2%)</td>
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<tr>
<td>Hypercholesterolemia</td>
<td>216(23.5%)</td>
<td>311(24.4%)</td>
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<tr>
<td>Low HDL-cholesterolemia</td>
<td>153(16.6%)</td>
<td>390(30.6%)</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>264(28.7%)</td>
<td>401(31.5%)</td>
</tr>
<tr>
<td>Smoker</td>
<td>392(42.6%)</td>
<td>465(36.5%)</td>
</tr>
<tr>
<td>Obesity</td>
<td>242(26.3%)</td>
<td>350(27.5%)</td>
</tr>
<tr>
<td>Family history</td>
<td>142(15.4%)</td>
<td>208(16.3%)</td>
</tr>
<tr>
<td>Coronary stenosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No stenosis</td>
<td>83.1%</td>
<td>0%</td>
</tr>
<tr>
<td>Single vessel</td>
<td>12.6%</td>
<td>36.7%</td>
</tr>
<tr>
<td>Multivessel</td>
<td>4.3%</td>
<td>63.3%</td>
</tr>
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HDL, high-density lipoprotein.
Smoking is closely associated with coronary spasm [17], but the mechanism(s) is still unclear. In animal models, cigarette smoke extract suppressed acetylcholine-induced, endothelium-dependent dilation, and this suppression was prevented by antioxidants or superoxide dismutase [18–20]. Thus, smoking reduces nitric oxide activity via oxygen-derived free radicals contained in cigarette smoke [21,22]. Both basal and acetylcholine-induced coronary endothelial dysfunction are improved by the intracoronary injection of vitamin C, an antioxidant, in patients with coronary spasm [23]. Vitamin E concentration is relatively low in patients with coronary spasm as compared with healthy subjects [24], and vitamin E administration is an effective treatment for coronary spasm [25]. Thus, administration of antioxidants in addition to conventional treatment is beneficial for coronary spasm.

Insulin resistance has been reported to play an important role in the pathogenesis of coronary heart disease [26,27]. Insulin causes endothelium-dependent vasodilation by releasing nitric oxide [28], and endothelium-dependent vasodilation is impaired in patients with insulin resistance [29]. Insulin sensitivity and endothelial function are decreased by cigarette smoking, and antioxidants such as vitamin C improve insulin sensitivity and endothelial function in smokers [30]. The decreased endothelium-dependent vasodilation observed in these subjects may result from the inactivation of endothelium-derived nitric oxide by reactive oxygen species [31]. The fasting glucose levels were not different between patients with coronary spasm and controls, whereas fasting insulin levels were higher in patients with coronary spasm than in controls [32]. Insulin sensitivity, as assessed by the steady state plasma glucose method, was impaired in patients with coronary spasm compared with controls. Antioxidants, such as vitamin C, can improve insulin sensitivity and endothelial function in patients with coronary spasm. Thus, reactive oxygen species and/or decreased nitric oxide bioactivity may play important roles in the genesis of both endothelial dysfunction and insulin resistance in patients with coronary spasm.

The endothelium plays an important role in the regulation of blood flow to insulin-sensitive tissues, and insulin induces endothelium-dependent vasodilation [28,32]. Reactive oxygen species cause endothelial dysfunction that may contribute to insulin resistance through impaired delivery of insulin to insulin-sensitive tissues such as skeletal muscle [33]. In addition, it is possible that reactive oxygen species may cause flow-independent insulin resistance by inhibiting insulin receptor signaling [34].

### Table 2  Precipitating factors for coronary spasm.

<table>
<thead>
<tr>
<th>Category</th>
<th>Factors</th>
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| 1. Physiological factors  | (1) Rest  
(2) Physical and emotional stress  
(3) Coronary spasm  
(4) Straining  
(5) Exposure to cold  
(6) Hyperventilation  
(7) Aging  
(8) Others |
| 2. Pharmacological agents | (1) Catecholamines (epinephrine/norepinephrine, dopamine/dobutamine, etc.)  
(2) Parasympathomimetic agents (acetylcholine, methacholine, etc.)  
(3) Anticholinesterase agents (physostigmine, neostigmine, etc.)  
(4) Ergot alkaloids (ergonovine, ergotamine, etc.)  
(5) Others (serotonin, prostaglandins, histamine, smoking, CaCl2, Tris-buffer, etc.) |
| 3. Genetic factors        |                                                                         |
Coronary smooth muscle in coronary spasm

Contraction of vascular smooth muscle depends on an increase of intracellular calcium ions [35]. Coronary smooth muscle of patients with coronary spastic angina shows a hypercontractile response to various stimuli such as acetylcholine or histamine [11,12,16,20,36]. This phenomenon may be caused by increased smooth muscle cell mass and/or increased receptor activation. Increased intimal thickening and hyperplasia of coronary arteries is involved in coronary spastic angina [37,38]. The phosphorylation of myosin light chain is the initial step for vascular smooth muscle contraction [35]. The contraction of coronary arteries occurs via Ca²⁺/calmodulin-activated myosin light chain kinase with subsequent phosphorylation of myosin light chain [35]. Myosin light chain phosphorylation is augmented in animal models with vascular spasm [39]. Rho-kinase augments myosin phosphorylation by inhibiting myosin phosphatase, leading to contraction of vascular smooth muscle [40]. Shimokawa and colleagues reported that protein kinase C and Rho-kinase activity were augmented in coronary smooth muscle of animal models with coronary spasm [41]. Thus, coronary spasm can also be regarded as a hypercontraction of coronary smooth muscle induced by an increase of intracellular calcium ions [42,43]. Calcium antagonists, which can block the entry of calcium ions into the cell, are very effective in suppressing coronary spasm [44].

Conclusions

Coronary spasm plays an important role in the pathogenesis of ischemic heart disease in general, including acute coronary syndromes. Acetylcholine, which is an endothelium-dependent vasodilator, can provoke coronary spasm possibly due to the presence of injured endothelium. Thus, patients with coronary spasm have a disturbance in endothelial function of the coronary arteries as well as a hypercontractile response of vascular smooth muscle. These findings suggest that vascular failure plays a crucial role in the pathogenesis of coronary spasm.

References


