

Research Progress on Coronary Microvascular Diseases

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Abstract: Coronary microvascular disease (CMVD) is a multifactorial myocardial ischemia-angina condition mainly stemming from abnormalities in the structure and function of coronary microvessels. Currently, there is no specialized treatment for CMVD. Therefore, enhancing research on CMVD can generate insights for subsequent clinical development of personalized treatments. This article delves into the research progress of CMVD and comprehensively reviews its definition, classification, epidemiology, pathological mechanisms, non-drug treatments, and advancements in Western medicine and traditional Chinese medicine approaches.

Keywords: Coronary microvascular-related diseases; Pathological mechanism; Research progress

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1. Introduction

The coronary microcirculation encompasses arterioles, venules, and capillaries, constituting a microvascular system. Coronary microvascular disease (CMVD) predominantly involves extravascular mechanisms, with exertional angina serving as the primary indicator, often indicative of myocardial ischemia^[1]. Principal manifestations of abnormal microcirculatory structure include reductions in vascular lumen diameter and microvessel density, leading to heightened microvascular resistance. Microcirculatory dysfunction manifests primarily through endothelial cell dependence, microvascular constriction, or embolism, alongside observable abnormalities in vasodilation^[2]. External compression and tissue edema represent prevalent signs of extravascular changes, sometimes accompanied by a reduction in cardiac diastolic time. This article presents a review of recent advancements in CMVD treatment research.

2. Definition and classification of CMVD

The etiology of CMVD is multifaceted, encompassing various clinical syndromes characterized by objective evidence of abnormal structure and/or function of coronary arterioles and arterioles. Predominant clinical features include exertional angina or myocardial ischemia, often predisposing individuals to coronary artery

disease. Decreases in coronary flow reserve (CFR) are common, with myocardial ischemia symptoms frequently accompanying angina attacks. CMVD can be classified based on causative factors into three types: (1) CMVD without obstructive coronary artery disease, (2) CMVD combined with obstructive coronary artery disease, and (3) other CMVD subtypes. CMVD without obstructive coronary artery disease encompasses microvascular angina and slow coronary flow, while CMVD combined with obstructive coronary artery disease primarily presents as stable angina due to coronary heart disease, with instances of vascular recanalization but persistent myocardial perfusion without reflows following emergency percutaneous coronary intervention (PCI). Other CMVD subtypes include mechanisms associated with stress-induced, hypertrophic, dilated cardiomyopathy, aortic stenosis, and other conditions.

3. Epidemiology of CMVD

CMVD patients exhibit a heightened risk of major adverse cardiovascular events (MACE) compared to healthy individuals. CMVD also serves as an independent risk factor for diastolic dysfunction, often necessitating hospitalization due to complications with heart failure with preserved ejection fraction. Hence, prompt and effective diagnosis and treatment of CMVD are imperative. Despite limited large-scale randomized controlled trials focusing on CMVD treatment, future studies should expand sample sizes to furnish high-quality evidence.

4. Pathological mechanisms of CMVD

4.1. Abnormal coronary microvascular structure

Abnormalities in the coronary microvascular structure entail pathological changes within the microvessels of the coronary artery system. These abnormalities may disrupt microcirculation, consequently affecting myocardial perfusion and cardiac function. Increased left ventricular mass can precipitate changes in vascular structure, leading to microvascular remodeling. In conditions like hypertrophic cardiomyopathy, smooth muscle cell hypertrophy and collagen deposition can cause intimal and medial hypertrophy in interval arterioles, thereby reducing the lumen area. Atherosclerosis can further exacerbate microvascular obstruction and lumen narrowing ^[3], resulting in structural abnormalities such as stenosis, blockage, or fibrosis within coronary microvessels. These aberrations impede myocardial perfusion and nutrient supply, potentially precipitating cardiac symptoms like chest pain, shortness of breath, palpitations, and in severe cases, cardiovascular events such as myocardial infarction.

4.2. Abnormal coronary microvascular function

Coronary microvascular dysfunction can arise from multiple factors, including endothelial dysfunction, inflammation, excessive contraction, and ischemia-reperfusion injury. It typically manifests as normal coronary arteries with impaired microvascular function, leading to myocardial ischemia and other cardiac complications. Patients may experience symptoms such as angina pectoris, chest pain, shortness of breath, and fatigue, often accompanied by endothelial or smooth muscle dysfunction, microvascular spasm, obstruction, and heightened inflammatory response.

- (1) Coronary endothelial dysfunction: This constitutes a pivotal factor in CMVD, wherein coronary endothelial cells, situated within coronary blood vessel walls, play a crucial role in vessel wall stability and function. Under normal conditions, endothelial cells regulate vessel relaxation and contraction by secreting bioactive substances, thereby maintaining vessel patency. Through the action of nitric oxide (NO), vascular endothelial cells can actively regulate vascular smooth muscle function, relax

large epicardial blood vessels and small blood vessels in the microcirculation, and promote increased coronary blood flow. However, in the presence of risk factors and atherosclerosis, endothelial cell damage and accelerated apoptosis occur, leading to endothelial dysfunction and impaired vasodilation response, subsequently affecting coronary blood flow.

- (2) Vasoactive substances: Stimulating smooth muscle in CMVD patients can disrupt cell membrane receptors and intracellular signaling pathways, contributing significantly to smooth muscle diastolic dysfunction.
- (3) Microvascular spasms: These spasms, often induced by sympathetic nerve dysfunction, can lead to a significant contraction of coronary microvessels, resulting in decreased myocardial perfusion and subsequently myocardial ischemia.
- (4) Inflammation and microvascular embolism: Inflammation serves as a crucial clinical indicator for CMVD prediction, with systemic inflammatory response potentially inducing CMVD ^[4].

5. Diagnostic technology of CMVD

5.1. Non-invasive techniques

Non-invasive technologies, such as transthoracic Doppler echocardiography (TTDE), myocardial contrast echocardiography (MCE), cardiovascular magnetic resonance (CMR), and positron emission tomography (PET), estimate CFR and evaluate microvascular function. PET testing serves as the gold standard with $CFR < 2$. CMR serves as the primary tool for assessing the myocardial perfusion reserve index (MPRI). Additionally, CMR technology can assess myocardial blood flow (MBF) under varying resting and hyperemic states, offering an alternative method for evaluating coronary microvascular function.

5.2. Invasive technologies

Coronary angiography provides insight into microvascular function, although the examination period may be affected by coronary perfusion pressure and heart rate. The thermodilution method evaluates coronary microvascular function but may yield biased results due to differences in saline injection dose and speed, as well as uneven mixing with blood. Intracoronary Doppler guidewires measure blood flow velocity and CFR within coronary arteries, but the guidewire's position may affect blood flow velocity.

6. Non-drug treatment

6.1. Lifestyle intervention

A heart-healthy diet, low in saturated fat and cholesterol but rich in fruits, vegetables, whole grains, and healthy fats (such as olive oil and nuts), is recommended. Maintaining a healthy weight reduces cardiac burden and improves microvascular function. Moderate aerobic exercise (e.g., walking, cycling, swimming) enhances heart blood supply, cardiovascular health, and microvascular function. Timely detection and management of chronic conditions like hypertension and hyperglycemia can curb microvascular disease progression. Effective stress management is crucial for cardiovascular health, as prolonged emotional stress may impair microvascular function.

6.2. Mechanical methods during percutaneous coronary intervention

Utilizing balloons, filters, and thrombus aspiration devices during interventional procedures can prevent distal embolism post-percutaneous coronary intervention (PCI), enhancing myocardial microcirculation, promoting

reperfusion, and mitigating myocardial infarction risk.

6.3. Ischemic adaptation

Repetitive cuff inflation and deflation on the upper arm induce local ischemia, prompting vasodilator-active factor release to safeguard the myocardium. Repeated balloon use pre- and post-PCI may induce significant changes in myocardial perfusion and infarction size, highlighting its potential in managing coronary artery obstruction and myocardial ischemia.

7. Western medicine treatment

7.1. Improving microvascular structure

PCI exhibits a positive impact on angina pectoris in CMVD patients with obstructive coronary artery disease, fostering favorable recovery in coronary microcirculation. Sodium nitroprusside, a commonly utilized drug for no-reflow treatment, dilates arterioles, enhancing coronary microcirculation blood flow. Anisodamine, a tropane alkaloid extracted from some plants of the family *Solanaceae*, mitigates microvascular spasms, regulates coronary microcirculation, prevents ischemia/reperfusion injury, reverses coronary no-reflow, and promotes positive myocardial blood flow ^[5]. Effective coronary microvessel expansion can be achieved during PCI. Injecting sodium nitroprusside and anisodamine into coronary arteries enhances myocardial microcirculation. Standardized nitrate drug use yields significant outcomes in subepicardial coronary artery stenosis and spasm-related conditions. Rho kinase inhibitor Fasudil reduces microvascular spasms and angina attack frequency, while Nicorandil dilates subepicardial coronary arteries, alleviating symptoms in coronary microvascular angina patients and improving electrocardiogram exercise test results. Ivabradine and Ranolazine also ameliorate angina pectoris symptoms. Reducing atherosclerosis risk factors can enhance treatment efficacy in patients with stable angina pectoris. Effective hypoglycemia restores coronary microvascular endothelial function. Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) alter endothelial function and decrease myocardial oxygen demand, prolonging diastolic perfusion in hypertension patients.

7.2. Anti-myocardial ischemia/angina pectoris

β -blockers significantly reduce myocardial oxygen consumption, slowing ventricular rate, prolonging ventricular diastole, increasing ventricular diastolic volume, and enhancing coronary perfusion when standardized. They also exhibit antioxidant properties. Combining β -blockers with non-dihydropyridine calcium antagonists synergistically improves efficacy. Nitrate drugs effectively treat subepicardial coronary artery stenosis, but their efficacy in CMVD treatment is limited due to their inability to interact with nitrate-converting enzymes and NO receptors. Calcium ion antagonist drugs, particularly non-dihydropyridine types, slow heart rhythms and alleviate myocardial ischemia symptoms. Dihydropyridine types relax blood vessels and myocardium, increasing blood oxygen demand and relieving chest pain. ATP-sensitive potassium channel opener Nicorandil dilates coronary microvessels, improving electrocardiogram exercise test results, especially suitable for treating coronary microvascular angina. Other drugs like late sodium channel blockers (e.g., ranolazine) improve angina symptoms, left ventricular diastolic function, and CFR. Sinoatrial node pacing current blocker Ivabradine serves as an alternative therapy for β -blocker-intolerant individuals. Rho kinase inhibitor Fasudil, when used properly, inhibits microvascular spasms, reduces angina frequency, and holds significant pharmaceutical value ^[6].

8. Traditional Chinese medicine treatment

8.1. Traditional Chinese medicine decoction

Research by Wang *et al.* has demonstrated that the Liqi Huatan Huoxue prescription can effectively protect vascular endothelium and alleviate clinical symptoms by increasing serum NO concentration ^[7]. Li and colleagues studied CMVD patients with qi stagnation and blood stasis, selecting Huoxue Tongmai Yixin Decoction to swiftly enhance cardiac microcirculation and restore vascular endothelial function, thereby reducing angina symptoms ^[8]. Zheng and the team advocate for nourishing the Qi meridians and unblocking the heart meridians to address microcirculatory disorders, improving cardiac blood supply, and alleviating CMVD symptoms ^[9].

8.2. Chinese patent medicines

Treatment with Xinkeshu Tablets, as studied by Chen *et al.* ^[10], increases NO expression and decreases endothelin-1 levels in patient serum, significantly improving treatment outcomes for coronary microcirculation disorders. Peng and colleagues found that the Huayu Fuyuan Capsule reduced inflammatory responses, and enhanced coronary microcirculation endothelial function and activity tolerance, thereby improving CMVD patients' quality of life ^[11].

8.3. Other TCM method of treatment

Acupuncture, as demonstrated by Zhang *et al.* ^[12], effectively treats angina pectoris with minimal adverse effects. Acupoint application of traditional Chinese medicine formulas positively influences angina pectoris prevention and treatment, regulating lipids, improving endothelial function, and demonstrating significant anti-inflammatory effects. Traditional Chinese medicine aerosol treatment for CMVD offers rapid onset, portability, and high safety. Studies indicate that wide-chest aerosol improves angina symptoms, enhances electrocardiogram efficacy, and is well-tolerated and safe for patients ^[13].

9. Conclusion

CMVD serves as a risk factor for coronary heart disease and cardiovascular events. Tailoring personalized treatment plans based on patient conditions is crucial. Traditional Chinese medicine holds potential advantages in CMVD prevention and treatment, although the complexity of traditional Chinese medicine ingredients necessitates further high-quality clinical observations in subsequent studies.

Disclosure statement

The author declares no conflict of interest.

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