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Rethinking on the pathogenesis, diagnosis and treatment of microvascular angina disease based on Chinese and foreign guidelines

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Abstract: *Microvascular angina is a common non obstructive coronary artery ischemic heart disease in clinical practice. Its diagnosis is often empirical and can be mistaken for symptoms caused by non-cardiac factors, leading to delayed progression. With the development and upgrading of modern diagnostic and treatment technologies, the pathogenesis, diagnosis and treatment of MVA are receiving increasing attention from clinical physicians. More and more studies have confirmed that coronary microcirculation plays an important role in myocardial ischemia. This article summarizes the pathogenesis and diagnosis and treatment recommendations of microvascular angina in relevant Chinese and foreign guidelines, hoping to provide new diagnosis and treatment ideas for microvascular angina.*

Keywords: *Microvascular angina; Coronary microvascular disease; Review*

1. Introduction

Microvascular angina (hereinafter referred to as MVA) refers to the syndrome with typical or atypical symptoms of angina pectoris, accompanied by objective evidence of myocardial ischemia, and excluding subepicardial obstructive coronary artery disease and other cardiovascular diseases. From the perspective of Pathophysiology, this disease is due to the pathological changes of the structure and function of the inferior myocardial coronary artery with a diameter of less than 500 microns [1]. With the continuous optimization of modern technology in coronary artery examination methods, the diagnostic rate of microvascular angina is also increasing. This article provides a review of the pathogenesis, diagnostic methods, and Western medicine treatment of microvascular angina, in order to provide diagnostic and therapeutic ideas for this disease.

2. Understanding of microvascular angina pectoris

In 1967, Likoff et al. reported a group of patients with typical labor angina pectoris, positive exercise test and normal coronary angiography, which was the first report of such diseases in History of medicine. Subsequently, in 1973, Kemp et al. [2] first named this condition X syndrome. In 1985, Cannon renamed this disease microvascular angina. In 2013, the European Society of Cardiology Guidelines for the Treatment of Stable Coronary artery disease, the disease was named as abnormal microvascular function. The Chinese expert group failed to include the structural abnormalities of this disease due to microvascular dysfunction, and therefore recommended renaming microvascular dysfunction to coronary microvascular disease (CMVD). In 2020, the European Society of Cardiology (ESC) and the European Society for Percutaneous Cardiovascular Intervention (EAPCI) jointly issued the "2020 European Expert Consensus on Non Obstructive Coronary Ischemic Disease (INOCA)", which refers to myocardial ischemia caused by coronary microcirculation disorders (CMD) as microvascular angina.

Due to limitations in diagnostic and treatment methods in the early stages, positive treadmill exercise tests are often used as a diagnostic basis for microvascular angina. With the development of diagnostic and treatment technology, people's understanding of such diseases has become clearer. In

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fact, microvascular angina can only be diagnosed if there is a coronary microcirculation disorder. However, microvascular angina is only a subtype of non-obstructive coronary ischemic heart disease, and there are many reasons that can cause non obstructive coronary myocardial ischemia, such as epicardial vasospasm, myocardial bridge, etc. [3].

3. The pathogenesis of microvascular angina

The pathogenesis of microvascular angina can be divided into two types: abnormal coronary microvascular function and microvascular structural remodeling [4]. Simply put, one is functional and the other is structural [5], and both can exist simultaneously.

3.1. Functional abnormalities

Abnormal function refers to abnormal vasomotor function of coronary artery microvessels. The main reasons are (1) injury of vascular endothelium: dysfunction of vasomotor function of vascular endothelial factor, which is manifested by decreased diastolic function and increased sensitivity to Vasoconstriction stimuli. Mainly due to abnormal production and release of endothelial dependent relaxing factor nitric oxide (NO) [6] Smooth muscle dysfunction: mainly because endothelial cell independent active factor stimulates receptors on smooth muscle cell membrane and intracellular signal pathways, thereby causing abnormal microvascular relaxation [7] Microvascular spasm: Some vasoactive substances can cause diffuse microvascular contraction and myocardial ischemia, but have no effect on the epicardial coronary artery. For example, the lack of estrogen level will affect the autonomic nervous function, and the dysfunction of autonomic nervous function will make the myocardium α abnormal activation of Adrenergic receptor causes coronary microvascular contraction, which leads to myocardial ischemia [8].

3.2. Structural abnormalities

Coronary microvascular remodeling can be divided into three types: centripetal remodeling of Arteriole, increase of vascular wall lumen ratio, decrease of myocardial capillary density, etc. [9]. The main reason may be: hypertensive ventricular hypertrophy, hypertrophic cardiomyopathy patients usually have the problem of hypertrophy of smooth muscle cells and excessive deposition of collagen fiber cells, which is easy to cause the thickening of vascular intima [10]. It is worth mentioning that the reconstructed Arteriole will become extremely sensitive to the stimuli of Vasoconstriction, which will lead to dysfunction of vasoconstriction. Its response to endothelial independent vasodilators (such as adenosine) can be manifested as a decrease in coronary flow reserve (CFR) and an increase in microcirculation resistance [11].

4. Risk factors

Traditional coronary heart disease risk factors such as hypertension, Dyslipidemia, smoking and diabetes may cause coronary microvascular disorders. (1) Hypertension: As mentioned earlier, hypertensive ventricular hypertrophy and hypertrophic cardiomyopathy can cause thickening of the intima of blood vessels, leading to the occurrence of microvascular structural abnormalities. Studies have shown that patients with microvascular angina have a significant increase in interventricular septal thickness compared to normal individuals, and the more significant the increase in interventricular septal thickness, the higher the risk of developing coronary microvascular angina [12] Dyslipidemia: Lipoprotein a is a risk factor of cardiovascular system. Studies have shown that the content of lipoprotein an in patients with microvascular angina is significantly higher than that in normal people, while apolipoprotein a is significantly lower. Apolipoprotein a may be a protective factor [13-16]. Some studies have also confirmed that lipoprotein associated Phospholipase A2 (Lp PLA 2) can promote the release of inflammatory factors, reduce the production of nitric oxide, and lead to dysfunction of coronary microvascular endothelial cells. A retrospective study by Zhang Yi and others found that the increase of serum Lp-PLA2 and homocysteine (Hcy) is an independent risk factor for coronary micro Vascular disease in middle-aged and elderly women [17].

In addition to traditional risk factors, risk variables related to inflammation also play a role in coronary microcirculation disorders [18,19]. Interleukin-1 (IL-1), Interleukin 6 (IL-6) tumor necrosis factor produced by microvascular smooth muscle cells- α (TNF- α) When inflammatory cells infiltrate,

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such growth factors and cytokines will cause abnormal proliferation and migration of smooth muscle cells [20]. Chen Bin et al. [21] monitored the high sensitivity C-reactive protein (hs-CRP) and coronary flow reserve (CFR) of 38 patients with microvascular angina using myocardial contrast echocardiography. The analysis results showed that the concentration of high sensitivity C-reactive protein was negatively correlated with coronary flow reserve.

Besides, compared with obstructive Coronary artery disease, social Psychological stress is more involved in the occurrence of non obstructive coronary ischemic heart disease. A meta-analysis showed a significant correlation between social and psychological factors and ischemic heart disease, including microvascular angina. In the female population with ischemic heart disease, patients are often accompanied by psychological disorders such as anxiety and depression [22]. Microvascular angina, as a common type of ischemic heart disease, often coexists with psychological disorders such as anxiety and depression [23].

5. Epidemiology

At present, there is no epidemiological data of coronary micro Vascular disease with large sample data in China. The past small sample clinical trials showed that the incidence rate of coronary microvascular disease was between 45% and 60% in patients with no obvious obstruction in coronary angiography when there were signs of myocardial ischemia. The incidence of microvascular angina in women is higher than that in men, especially in perimenopausal women [24,25].

6. Western medicine diagnosis and treatment plan for microvascular angina

6.1. Diagnostic indicators

Based on the diagnostic protocols provided in Chinese and foreign guidelines, it is divided into invasive assessment and non-invasive assessment. At present, there is no direct method for observing human coronary microcirculation, and the existing evaluation indicators mainly rely on functional indicators: (1) CFR Coronary Flow Reserve refers to the ratio of the average peak flow rate in the maximum congestive state to the resting average peak flow rate under the action of various vasoactive stimuli (such as adenosine). It comprehensively reflects the blood flow status of the epicardial coronary artery and coronary artery microcirculation. The normal value of CFR is 3-5, and less than 2 indicates insufficient myocardial perfusion. (2) Index of Microcirculatory Resistance (IMR) refers to the distal coronary artery pressure under maximum congestion × Average conduction time in congested state. IMR ≥ 25 indicates microvascular dysfunction. (3) Fractional flow reserve (FFR) is the ratio of distal coronary artery mean pressure to aortic pressure in congested state, which can be used to evaluate whether blood flow is restricted in patients with obstructive coronary heart disease. FFR ≤ 0.8 indicates abnormalities.

6.1.1. Invasive assessment

It includes guide wire direct invasion test and Acetylcholine excitation test. Diagnostic options include thermaldilution and Doppler technology based guidewire. There is evidence to suggest that the Doppler may better reflect the state of insufficient microvascular perfusion than the thermaldilution [26]. Currently, the intracoronary Doppler flow guidewire is the gold standard for measuring CFR in traumatic techniques.The invasive diagnostic criteria for microvascular angina given in the guidelines are: diagnostic guide wire and adenosine test: FFR>0.8 (non-obstructive)+CFR<2.0, IMR ≥ 25 (microcirculation disorders)+Acetylcholine provocation test: no or<90% of the internal diameter decreases, angina symptoms, ischemic ECG changes (indicating that there is myocardial ischemia without epicardial vasospasm).

6.1.2. Non invasive assessment

A variety of non-invasive techniques, including ECG exercise tolerance test, transthoracic Doppler echocardiography (TTDE), myocardial contrast echocardiography (MCE), myocardial perfusion imaging, Positron emission tomography (PET), and cardiac magnetic resonance imaging (CMR), can be used to detect local myocardial ischemia. PET is considered as a non-invasive gold standard for the diagnosis of coronary micro Vascular disease due to its high accuracy. Myocardial contrast-enhanced echocardiography (MCE) is widely used in clinical practice due to its real-time bedside operation, relatively low cost, and ability to quantitatively and qualitatively evaluate myocardial blood flow

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perfusion. The non-invasive diagnostic criteria provided in the guidelines are: objective evidence of myocardial ischemia in resting or under load conditions exists, and CFR values<2.0 are measured and calculated using non-invasive examination equipment to illustrate coronary microcirculation disorders; If CFR ≥ 2.0, the stimulation test of Acetylcholine is feasible. If there is no spasm of the epicardial coronary artery but angina pectoris symptoms and ECG blood deficiency ST-T changes occur, microvascular angina pectoris can also be diagnosed.

6.2. Medicine Treatment

6.2.1. Traditional treatment:

(1) Control of risk factors: angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) are the first choice for patients with hypertension, statins can be used for patients with hypercholesterolemia, active control of blood glucose in patients with diabetes can improve coronary microvascular endothelial function, and obesity can improve CFR by weight loss [27]; (2) Improvement of myocardial ischemia: drugs for stable microvascular angina are mainly used to reduce myocardial oxygen consumption, such as β-blockers. If β-blockers are not tolerated, ivabradine can be used instead [28].Drugs such as ACEI, ARB, and ranolazine have the effect of increasing CFR values and improving small vessel remodeling. For perimenopausal female patients with stable microvascular angina, estrogen supplementation can be combined. At present, studies [29] have reported that endothelial function is impaired in postmenopausal women with microvascular angina, and administering exogenous estradiol can increase peripheral blood flow in normal postmenopausal women. Calcium antagonists are recommended for angina pectoris, which is mainly caused by microvascular spasm. Nicorandil can effectively dilate subepicardial coronary arteries and coronary Arteriole, so it should be the first recommended drug for coronary microvascular angina [30].

6.2.2. New Drug Treatments

(1) Long term supplementation (6 months) of L-arginine (a precursor of NO) can improve endothelial function, coronary blood flow, and symptoms in non-obstructive CAD patients, but does not include CFR Oral administration of selective ETA receptor antagonist (Zibotan) can antagonize endothelin-1 induced Vasoconstriction, thereby improving vascular endothelial function [31]. (3) Phosphodiesterase is highly expressed in vascular smooth muscle cells, and inhibiting its secretion can promote vascular smooth muscle relaxation. Oral Phosphodiesterase inhibitor can rapidly increase CFR value of patients, and has anti-inflammatory and antiplatelet effects [32].

7. Etiology, pathogenesis and treatment of traditional Chinese medicine

There is no name for microvascular angina in traditional Chinese medicine, and there is currently no unified classification. According to its clinical symptoms, it should be classified into categories such as "chest pain" and "heartache". It shares similarities with traditional chest pain, but also has different characteristics. MVA patients are often associated with collateral obstruction. Traditional Chinese medicine believes that the causes of MVA related collateral lesions include the following four points: (1) the collateral itself is thin and curved, resulting in delayed circulation of qi and blood, which is prone to pathological changes of stasis [33]; (2) The pathogenic factors of phlegm and dampness in the blood are often sticky and greasy, which can easily stagnate in the collaterals, leading to poor circulation of qi and blood in the veins Due to external cold pathogenic factors, the heart yang is insufficient, and the cold pathogenic factors of the six evils have the characteristics of attracting and stagnating. Therefore, the two colds interact with each other, causing the collaterals of the heart to be congested and urgent, and the qi and blood to be blocked [34] Qi is the leader of blood, and the operation of blood in the collaterals mainly depends on the promotion of qi. If Psychological stress is too high, anxiety and gas stagnation may occur, which may lead to unfavorable operation of qi, inability to promote blood operation, and blocked collaterals. Wu Yiling, an expert in collateral diseases in China, pointed out that according to the "theory of pathological changes in the venation vascular system", the concepts of venation, middle and small arteries, and microcirculation are highly consistent, so the abnormal function of the collateral homeostasis is similar to the vascular endothelial dysfunction called by modern medicine. Collateral deficiency is a state of contraction, contraction, and spasms caused by various factors such as external pathogens, excessive emotions, and overwork. It is one of the main pathological changes in collateral diseases. Modern medicine believes that a decrease in NO concentration and an increase in ET concentration in blood vessels are one of the pathological foundations of coronary artery spasm and endothelial dysfunction [35]. The urgency of collaterals is

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basically similar to the vasospasm in modern medicine, and vascular endothelial dysfunction and vasospasm can lead to blood hypercoagulability, microthrombosis formation, and even myocardial ischemia and necrosis [36]. This is consistent with the theory of "phlegm stasis obstructing collaterals" in traditional Chinese medicine. In summary, phlegm turbidity, qi stagnation, and blood stasis are the basic characteristics, so in terms of treatment, the characteristics of traditional Chinese medicine are to regulate qi, dissipate phlegm, and promote blood circulation and unblock collaterals.

8. Summary and Outlook

In summary, with the development of modern diagnostic and treatment technologies, the relevant pathogenesis and diagnosis and treatment plans of microvascular angina have become increasingly perfect, gradually evolving from the initial "X syndrome" to the widely recognized "microcirculation function and structural disorders". However, many underlying mechanisms have not yet been fully elucidated, and further development and popularization of modern diagnostic and treatment technologies are needed. More and more studies show that microvascular angina plays an important role in non-obstructive ischemic heart disease, and is closely related to cardiovascular diseases such as hypertrophic cardiomyopathy, diabetes heart disease and hypertensive heart disease. Therefore, the prevention and treatment of microvascular angina is an important issue that urgently needs attention. We hope to raise the attention of clinical colleagues to microvascular angina disease through this discussion, update relevant concepts, and conduct large-scale epidemiological investigations if necessary to optimize diagnostic plans and form a more standardized and complete diagnosis and treatment system.

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