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Exploration on the Pathogenesis and Treatment of Microvascular Angina Pectoris Based on the Theory of "Xuqi Liuzhi"

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Abstract: Microvascular angina (MVA) is an ischemic chest pain syndrome caused by coronary microvascular dysfunction (CMD). It is a subtype of non-obstructive coronary artery disease (INOCA). Its clinical manifestations are highly consistent with the 'chest pain' of traditional Chinese medicine. Based on the theory of 'deficiency and qi stagnation', combined with the pathological correlation between this theory and MVA and the modern pharmacological mechanism, this paper discusses the pathogenesis and treatment of MVA. The key of this disease is deficiency in origin and excess in superficiality, 'deficiency qi' is the basis of pathogenesis, and deficiency of both heart and kidney is the basis; 'Retention' is the sign of the disease, with blood stasis, phlegm turbidity and other stagnation of heart collaterals as the sign. The treatment is based on the basic principle of 'tonifying deficiency and promoting stagnation'. The specific treatment method is to correct the deficiency of heart and kidney qi by replenishing qi and nourishing heart, tonifying kidney and consolidating root, etc., combined with the method of promoting blood circulation and removing blood stasis, removing phlegm and dredging collaterals to remove blood stasis and phlegm turbidity, so as to provide a new path for the diagnosis and treatment of MVA in traditional Chinese medicine.

1. Introduction

Microvascular angina (MVA) refers to recurrent exertional chest pain with objective evidence of chronic myocardial ischemia and decreased coronary flow reserve (CFR). Low, and coronary angiography excludes a clinical disease with significant stenosis of subepicardial vessels[1], accounting for 45% -60% of non-obstructive coronary artery disease (INOCA)[2]. Studies have shown that MVA is closely related to the occurrence of a variety of adverse cardiovascular events, including angina pectoris, myocardial infarction, stroke and even death[3-4]. Modern medical treatment of MVA is mainly to control risk factors and relieve myocardial ischemia symptoms. Anti-angina pectoris drugs such as nicorandil and trimetazidine are commonly used, but there are individual differences in efficacy, and it is difficult to reverse microvascular structure and function damage[5]. Traditional Chinese medicine has unique advantages in the prevention and treatment of MVA, which can effectively alleviate the symptoms of angina pectoris and reduce the incidence of adverse cardiovascular events[6].

The theory of 'Xuqi Liuzhi' from the theory of 'Renzhai Zhizhi Fanglun·Zhangman' written by Yang Shiying in the Song Dynasty: 'The virtual person, when the bloating is reduced, the deficiency and qi stagnation', which was deepened by academician Wang Yongyan. It is clear that qi stagnation, blood stasis and phlegm turbidity are caused by deficiency of primordial qi, thus blocking the pathological process of meridians[7-8]. Clinical studies have confirmed that MVA patients generally have 'heart and kidney qi deficiency' syndromes, such as chest tightness, shortness of breath, palpitations, fatigue, soreness and weakness of waist and knees, as well as the symptoms and signs of 'blood stasis and phlegm turbidity' such as stabbing pain in the precardiac area, dark purple tongue, and greasy tongue coating. The pathological process is highly consistent with the pathogenesis of 'deficiency qi stagnation'. Therefore, based on the theory of 'deficiency and qi stagnation', this paper discusses the pathogenesis of MVA, and puts forward that 'tonifying deficiency and stagnation' is the basic principle for the treatment of MVA. The traditional Chinese medicine treatment of MVA provides theoretical support and practical reference.

2. The theory of "Xuqi Liuzhi" and MVA

2.1 "Xuqi"-heart and kidney deficiency is the pathogenesis of MVA

"Xuqi" refers to the deficiency of qi in the viscera, especially the deficiency of heart qi and kidney qi, which is the root of the disease. "Suwen·Weilun" points out that: "Heart governs the blood vessels of the body", indicating that abundant heart qi is the fundamental driving force for blood circulation; as the congenital foundation, kidney mainly stores essence, and essence can produce blood and transform qi. The warm function of kidney qi is the driving force for heart qi to be launched. The two organs of heart and kidney construct the fundamental support of life activities through 'water and fire' and 'essence and blood homology'. The filling of the two organs directly determines the running state of qi and blood. Heart qi deficiency leads to weak blood supply, kidney qi deficiency leads to gasification without power, and kidney yang warming function decreases. Clinically, MVA patients have aggravated chest pain, shortness of breath, weak tongue, pale tongue, cold hands and feet, and soreness and weakness of waist and knees.

Modern medicine believes that vascular endothelial dysfunction is a key link in the pathogenesis of MVA. Vascular endothelium can generate a variety of vasoactive compounds, such as nitric oxide, prostacyclin, endothelial-derived hyperpolarizing factor and other diastolic substances, and endothelin, thromboxane A2 and other contraction substances, through different mechanisms to regulate small artery vasomotor tension and maintain microvascular homeostasis[9]. Vascular endothelial function damage is closely related to heart and kidney deficiency. Studies have shown that heart qi can regulate the contraction and relaxation of vascular channels and affect the energy metabolism of myocardial cells[10]. The decrease of myocardial contractility caused by heart qi deficiency leads to insufficient coronary perfusion pressure, microvascular hemodynamic disorder, and decreased activity of vascular endothelial cells due to ischemia and hypoxia[11]. Kidney qi deficiency can lead to the attenuation of hormone levels in the elderly, and destroy the homeostasis of lipid metabolism by affecting the hypothalamus-pituitary-target gland axis (HPTA), thereby aggravating ox-LDL deposition and promoting atherosclerotic plaque formation. At the same time, it aggravates oxidative stress damage to vascular endothelium[12]. Aging is closely related to microcirculation disorder[13]. MVA patients have heart and kidney deficiency due to old age, excessive fatigue or long-term illness, and the abnormal physiological function corresponding to heart and kidney qi deficiency is an important pathological mechanism leading to cardiovascular disease[14-15]. This ' phlegm turbidity and blood stasis ' is an important part of 'Liuzhi'.

2.2 "Liuzhi"-Blood stasis and phlegm are the symptoms of MVA

"Liuzhi" is not only a pathological product such as blood stasis and phlegm turbidity, but also a "substantial pathogen" that directly causes obstruction of the cardiac collaterals and induces pain. Corrections of Errors in Medical Works clearly states: "When primordial qi is deficient, it will inevitably fail to reach the blood vessels; without qi, blood will stagnate in the vessels". The lesion of MVA (Microvascular Angina) is located in the minute collaterals of the heart, which are prone to deficiency, stagnation, and blockage[16]. Deficiency of heart and kidney qi weakens the functions of promotion and warming, resulting in slow or even stagnant blood flow in the tiny collaterals, and thus easily forming micro-level blood stasis. Su Wen (Plain Questions)records: "The kidney is the organ of water and governs body fluids". Su Wen·Treatise on Water and Heat Acupoints states: "The kidney is the gateway of the stomach; when the gateway fails to function properly, water accumulates and follows its inherent nature". Complete Works of Jingyue also notes: "Phlegm transformation occurs everywhere, yet the root of phlegm lies in the kidney". These indicate that the kidney's function of steaming and transforming qi dominates the transportation and excretion of body fluids throughout the body. Kidney qi deficiency impairs the transforming function, leading to internal retention of water-dampness; heart qi deficiency fails to disperse chest yang, causing body fluids to deviate from normal metabolism and accumulate into phlegm. As a yin pathogen, phlegm turbidity is sticky in nature. Once formed, it is most likely to block qi movement. Obstruction of the heart's minute collaterals by phlegm turbidity further hinders the circulation of qi and blood, exacerbating the state of "stagnation. " Phlegm and blood stasis often intermingle: phlegm obstruction impedes blood flow, while blood stasis promotes phlegm production, jointly blocking the cardiac collaterals. Blood stasis is characterized by fixed chest pain, dark purple tongue or ecchymoses on the tongue, and cyanosis of the lips. Phlegm turbidity is manifested as severe chest stuffiness with relatively mild pain, obesity, greasy tongue coating, and slippery pulse.

Studies have revealed that coronary microvascular dysfunction is an important factor contributing to the pathogenesis of MVA[17], and coronary endothelial cells play a key role in maintaining coronary microvascular function. Dysregulation of glucose and lipid metabolism, especially the oxidation of low-density lipoprotein cholesterol (LDL-C) and the accumulation of triglycerides, can induce coronary endothelial cell injury by triggering inflammatory responses[18]. Long-term endothelial cell injury can initiate and amplify the body's coagulation response by releasing specific procoagulant factors, such as von Willebrand Factor (vWF) and fibrinogen, thereby leading to the formation of microthrombi[19]. The core inducement of this abnormality is closely related to pathological products such as "blood stasis" and "phlegm turbidity" in traditional Chinese medicine (TCM). TCM holds that phlegm turbidity corresponds to the body's glucose and lipid metabolism disorders[20], and blood stasis is closely associated with platelets, the coagulation system, and the fibrinolytic system[21]. These "phlegm turbidity" and "blood stasis" are important components of "stagnation".

3. The treatment principle of MVA

Based on the theory of "Xuqi Liuzhi" and combined with the pathological basis of heart-kidney deficiency as the root cause, and blood stasis and phlegm turbidity as the manifestations, the treatment should take "tonifying deficiency and relieving stagnation" as the core principle. For heart-kidney deficiency, medicines such as Ginseng and Astragalus can be used to greatly tonify primordial qi, improving collateral stasis caused by qi deficiency at the source. Medicines including Eucommia Ulmoides, Achyranthes Bidentata, Morinda Officinalis, Prepared Polygonum Multiflorum, and Lycium Barbarum nourish the liver and kidney, replenish essence and blood, and consolidate the root and cultivate primordial qi. They support heart qi through the innate foundation (kidney),

fundamentally improving the state of insufficient blood circulation due to qi deficiency. For the pathological products of "stagnation", medicines like Salvia Miltiorrhiza, Panax Notoginseng, Trichosanthes Kirilowii, and Pinellia Ternata are selected to promote blood circulation to remove blood stasis, resolve phlegm and unblock collaterals, thereby relieving angina symptoms. Overall, the treatment takes promoting blood circulation and resolving phlegm as the means, and tonifying the heart and kidney as the foundation. Together, it exerts the effects of replenishing qi and nourishing the heart, tonifying the kidney and consolidating the root, promoting blood circulation to remove blood stasis, and resolving phlegm to unblock collaterals, accurately targeting the core pathogenesis of "deficient qi causing stagnation" in microvascular angina.

3.1 Tonifying Deficiency

3.1.1 Replenishing Qi to Nourish the Heart

For insufficient heart qi, qi-tonifying medicines such as Ginseng and Astragalus are selected to enhance myocardial contractility and improve coronary perfusion. Representative formulas include Yangxin Decoction (Heart-Nourishing Decoction) and Buzhong Yiqi Decoction (Middle-Jiao-Tonifying and Qi-Invigorating Decoction). Modern pharmacological studies have shown that the main components of Ginseng can improve myocardial energy metabolism, exert anti-inflammatory, antioxidant, and vasodilatory effects [22]. Ginsenoside Rg1, the core active component of Ginseng, can promote endothelial progenitor cells to secrete exosomes containing VEGF, which not only improves myocardial energy metabolism but also enhances angiogenic capacity. Additionally, ginsenoside Rg1 can stimulate endothelial progenitor cells to secrete exosomes loaded with angiogenesis-related proteins, thereby accelerating angiogenesis[23]. Astragaloside IV and Astragalus polysaccharides, the active components of Astragalus, can protect cardiac function by inhibiting myocardial cell apoptosis, regulating cellular signaling pathways, and suppressing cardiac hypertrophy. They also reduce cellular inflammatory responses, promote angiogenesis, protect vascular endothelial cells, and maintain the stability of their junctions[24]. The synergistic effect of these two medicines can better improve the structural integrity and functional state of myocardial cells, laying a myocardial functional foundation for the blood supply needs of microvessels.

3.1.2 Tonifying the Kidney to Consolidate the Root

For insufficient kidney qi, medicines such as Eucommia Ulmoides, Achyranthes Bidentata, Morinda Officinalis, Polygonum Multiflorum, and Lycium Barbarum are selected. Studies have shown that Eucommia Ulmoides[25] can effectively regulate blood glucose and lipid levels, improving glucose and lipid metabolism. Achyranthes Bidentata[26] can promote angiogenesis by enhancing the homing, survival, and proliferation of bone marrow mesenchymal stem cells. Extracts of Morinda Officinalis not only effectively inhibit LPS-induced NO production, reduce the content of inflammatory mediator PGE, and alleviate inflammation-mediated microvascular endothelial injury and aggravated stagnation, but also its active component, morinda officinalis oligosaccharides, has significant pro-angiogenic activity. It can promote myocardial microangiogenesis, improve blood supply to ischemic areas, and relieve angina symptoms[27]. Stilbene glycoside in Polygonum Multiflorum exerts antioxidant and anti-inflammatory effects, which can reduce vascular endothelial injury and produce a significant vasodilatory effect on blood vessels[28]. Lycium barbarum polysaccharides (LBP) abundant in Lycium Barbarum and anthraquinone components in Prepared Polygonum Multiflorum have significant immunomodulatory and antioxidant activities. LBP can improve the inflammatory injury state of vascular endothelium and delay the progression of microangiopathy by inhibiting inflammatory factors such as IL-6 and TNF-α[29]. Through regulating

metabolism, anti-inflammation, and antioxidation, these medicines fundamentally improve the pathological state of "kidney qi exhaustion leading to dysfunction of qi transformation", providing guarantee for the recovery of microvascular function. This echoes the TCM theory that "the kidney governs qi transformation", strengthening the theoretical connection between "tonifying the kidney to consolidate the root" and "microvascular repair".

3.2 Relieving Stagnation

3.2.1 Promoting Blood Circulation to Remove Blood Stasis

For pathological products such as blood stasis, blood circulation-promoting and stasis-removing medicines including Salvia Miltiorrhiza, Ligusticum Chuanxiong, Carthamus Tinctorius, Panax Notoginseng, and Moutan Cortex are selected to precisely target microvascular dysfunction. Tanshinone IIA in Salvia Miltiorrhiza can significantly upregulate the expression of endothelial nitric oxide synthase (eNOS) in vascular endothelial cells, promote the production of nitric oxide (NO), and correct the imbalance of vascular vasomotor function[30]. Panax Notoginseng, through its core active components (such as saponins including Notoginsenoside R_1, Ginsenoside Rg_1, and Rb_1), can improve blood rheology, reduce blood viscosity, and inhibit platelet aggregation to alleviate microvascular stagnation. Meanwhile, it promotes angiogenesis, repairs damaged microvascular endothelium, improves myocardial microcirculatory perfusion, and protects microvascular structure and function by inhibiting inflammatory factors such as TNF-α and resisting oxidative stress, thereby relieving angina symptoms[31].

Ligusticum Chuanxiong contains a variety of active components. Among them, Tetramethylpyrazine can regulate vascular vasomotion by inhibiting calcium ion influx, reducing endothelin-1 content, and increasing NO production; Z-ligustilide can promote angiogenesis in microvascular endothelial cells, reduce blood viscosity, and inhibit platelet aggregation to decrease microvascular stagnation. Its multiple components exert anti-inflammatory and analgesic effects, alleviating microvascular inflammation by inhibiting the release of inflammatory factors such as TNF-α and regulating inflammatory pathways like NF-κB, thus improving myocardial microvascular blood supply[32]. Extracts from Carthamus Tinctorius can inhibit oxidative stress and reduce the release of inflammatory factors by activating the PI3K/mTOR pathway, alleviating myocardial ischemic injury. On one hand, Hydroxysafflor Yellow A can inhibit vascular endothelial cell apoptosis, improve lipid metabolism, and reduce the risk of microvascular stagnation; on the other hand, Safflor Yellow can inhibit platelet aggregation, regulate thromboelastography indicators to resist thrombosis, dilate blood vessels, lower blood pressure, and improve myocardial microvascular perfusion. Additionally, its antioxidant effect can scavenge free radicals and protect microvascular structure[33]. Paeonol, the active component of Moutan Cortex, can regulate the balance of vascular vasomotion to improve microvascular perfusion. It protects microvascular endothelium by reducing ox-LDL and inhibiting ox-LDL-induced adhesion of vascular endothelial cells and expression of inflammatory factors, thereby improving lipid metabolism and resisting atherosclerosis to delay microangiopathy[34]. Xuefu Zhuyu Decoction (Blood-Stasis-Removing Decoction), a commonly used clinical representative formula, can promote angiogenesis by effectively inhibiting inflammatory responses and oxidative stress, improve atherosclerotic lesions, and enhance plaque stability[35].

3.2.2 Resolving Phlegm to Unblock Collaterals

For phlegm turbidity, phlegm-resolving medicines such as Trichosanthes Kirilowii, Allium Macrostemon, Pinellia Ternata, and Citrus Reticulata Peel are selected to improve metabolic

disorders and eliminate lipid deposition in vascular walls. Experimental studies have confirmed that quercetin contained in Trichosanthes Kirilowii can effectively reduce blood glucose levels in diabetic mice, and lower the incidence of cardiovascular diseases by downregulating the expression of TGFβ1 gene and protein[36]. Trichosanthes Kirilowii, Allium Macrostemon and Pinellia Ternata Decoction is a representative formula: the combination of Trichosanthes Kirilowii and Allium Macrostemon can effectively promote fat metabolism and decomposition, regulate glucose and lipid metabolism disorders, and protect damaged myocardium through anti-inflammatory effects[37]. Additionally, studies have shown that Erchen Decoction (Two-Chen Decoction) can effectively reduce blood lipid levels and protect vascular endothelium by resisting oxidative stress[38]. Formulas for regulating qi, resolving phlegm and promoting blood circulation can improve coronary microcirculatory disorders and the formation of coronary microvascular thrombosis, thereby reducing the risk of coronary microvascular thrombosis[39].

4. Conclusion

The core pathogenesis of microvascular angina (MVA) is "deficient qi causing stagnation", characterized by heart-kidney qi deficiency as the root cause and blood stasis and phlegm turbidity as the manifestations. The pathological cycle of "deficiency-stagnation-pain" is the key to the occurrence and progression of the disease. Correspondingly, the therapeutic method of "Tonifying Deficiency and Relieving Stagnation" improves the state of qi deficiency through "Replenishing Qi to Nourish the Heart and Tonifying the Kidney to Consolidate the Root", and eliminates pathological products via "Promoting Blood Circulation to Remove Blood Stasis and Resolving Phlegm to Unblock Collaterals". This approach can effectively restore microvascular perfusion and alleviate myocardial ischemia. The "Tonifying Deficiency and Relieving Stagnation" method not only reflects the advantage of the TCM treatment principle of "treating both the root cause and manifestations" but also provides theoretical and experimental support for the prevention and treatment of MVA with integrated traditional Chinese and Western medicine through modern pharmacological research.

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