

Progress in the Integrated Traditional Chinese and Western Medical Diagnosis and Treatment of Microvascular Angina and Research into Its Modern Pharmacological Mechanisms

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Abstract: Microvascular angina (MVA) is an ischaemic heart disease characterised by coronary microvascular dysfunction (CMD). With continuous advances in coronary functional testing, the diagnostic and therapeutic approach to MVA has gradually shifted from a process of exclusion to mechanism-based classification and personalised treatment. Currently, modern medicine primarily relies on the control of risk factors and pharmacological treatment targeting specific subtypes of microcirculatory abnormalities; however, some patients continue to suffer from recurrent symptoms and a reduced quality of life. In Traditional Chinese Medicine (TCM), this condition falls under the categories of ‘chongbi’ and ‘xintong’, indicating that its core pathogenesis involves ‘deficiency at the root and excess at the branch’ and ‘obstruction of the heart meridians’. Clinical treatment approaches predominantly focus on methods such as tonifying qi, promoting blood circulation, regulating qi and resolving phlegm. Existing evidence suggests that the use of Chinese herbal medicines or proprietary Chinese medicines in combination with conventional treatment helps to improve angina symptoms and certain microcirculatory and endothelial function indicators. The mechanisms of action may involve the regulation of the endothelial nitric oxide synthase/nitric oxide (eNOS/NO) pathway, the suppression of inflammatory and oxidative stress responses, and the intervention in myocardial fibrosis; however, the overall quality of evidence from existing studies remains limited. This article analyses and explains the modern medical understanding of MVA, its TCM pattern differentiation, integrated Chinese and Western medical treatment, and modern pharmacological mechanisms, whilst also exploring future research directions.

1. Introduction

Microvascular angina (MVA) is an important clinical phenotype of ischaemic heart disease, the occurrence of which is closely associated with structural or functional abnormalities in the coronary microvasculature. According to the COVADIS international criteria [1], the diagnosis of MVA is primarily based on four aspects: the presence of ischaemia-related symptoms, the absence of obstructive coronary artery disease, objective evidence of myocardial ischaemia, and the presence of coronary microvascular dysfunction. In this context, non-occlusive coronary artery disease typically refers to coronary artery stenosis of <50 per cent and/or a fractional flow reserve (FFR) >0.80 [1,2]. As understanding of the pathophysiological mechanisms underlying non-obstructive coronary arteries (ANOCA/INOCA) continues to deepen, the 2024 European Society of Cardiology (ESC) Guidelines on Chronic Coronary Syndrome have further incorporated MVA into the spectrum of angina/ischaemia with ANOCA/INOCA, emphasising the identification of different pathophysiological subtypes—such as endothelial dysfunction, impaired microvascular dilation and microvascular spasm—during clinical assessment [3].

It is worth noting that the incidence of MVA is significantly higher in women, and its clinical prognosis is not benign. Data from the international COVADIS prospective cohort study indicate that patients with MVA remain at risk of major adverse cardiovascular events during follow-up; this suggests that long-term management strategies should not be limited to the relief of chest pain symptoms, but must also take into account the control of risk factors, the improvement of microcirculatory function and the enhancement of quality of life [4]. Building on this, the 2025 ANOCA/INOCA clinical criteria consensus published by the COVADIS expert panel further emphasised that pathophysiological subtypes should be identified based on coronary functional abnormalities, and that standardised, patient-centred diagnostic and treatment pathways should be established [5].

Currently, the treatment of MVA is gradually shifting from empirical anti-anginal therapy towards individualised management based on pathophysiological subtyping; however, treatment responses to drugs such as beta-blockers, calcium channel blockers, ACEIs/ARBs and reserpine vary among patients [3,4]. In China, traditional Chinese medicine (TCM) has been widely applied in the clinical management of MVA and coronary microvascular disease (CMVD), and relevant guidelines, expert consensus and clinical studies are continually accumulating [6-9]. Against this backdrop, how to evaluate the actual clinical benefits of TCM within a unified modern medical diagnostic framework, and to further explore the relationship between TCM syndromes and objective, reproducible microcirculatory indicators, are key issues requiring focus in current research on the integration of Chinese and Western medicine.

2. Modern Medical Understanding and Advances in the Diagnosis and Treatment of MVA

2.1 Definition

MVA refers to the clinical manifestations of myocardial ischaemia caused by structural or functional abnormalities in the coronary microvasculature. According to the COVADIS criteria, the diagnostic criteria for MVA include ischaemia-related symptoms, objective evidence of myocardial ischaemia, the absence of obstructive coronary artery disease, and coronary microvascular dysfunction; the absence of obstructive coronary artery disease typically refers to coronary artery stenosis $<50\%$ and/or an FFR >0.80 [1-3]. The 2024 ESC Guidelines further recognise MVA as an important pathophysiological subtype of ANOCA/INOCA, the mechanisms of which may manifest as impaired coronary microcirculatory diastolic reserve, increased microvascular resistance and/or abnormal contraction of coronary microarteries [4].

2.2 Pathophysiological Mechanisms

2.2.1 Functional microvascular abnormalities

The coronary microcirculation plays a vital role in regulating resistance to myocardial blood flow. Patients with MVA may exhibit impaired endothelium-dependent or non-endothelium-dependent relaxation. Endothelial dysfunction can lead to reduced NO bioavailability and a relative increase in the effects of vasoconstrictor mediators; insufficient relaxation reserve in response to stimuli such as adenosine may manifest as reduced CFR. In addition, some patients experience chest pain and ischaemic ECG changes during acetylcholine stimulation, yet show no obvious epicardial vasospasm, suggesting microvascular spasm [3,4,10]. These mechanisms may occur independently or coexist in the same patient.

2.2.2 Structural microvascular abnormalities

Factors such as long-term hypertension, diabetes, dyslipidaemia, ageing and chronic inflammation may promote microarterial wall thickening, luminal remodelling, capillary sparsity and perivascular fibrosis, leading to an increase in minimum microvascular resistance and limiting the increase in blood flow during hyperaemia [4,10]. Structural CMD cannot be identified by coronary angiography alone; its clinical phenotype is usually inferred by combining functional indicators such as CFR and microcirculatory resistance.

2.2.3 Inflammation, Oxidative Stress and Autonomic Factors

Inflammatory responses and oxidative stress are key contributing factors in the onset and progression of CMD; they influence coronary microcirculation by reducing NO bioavailability, damaging the vascular endothelium and promoting vascular remodelling. In addition to local vascular mechanisms, early studies on cardiac X syndrome also revealed that some patients exhibit autonomic dysfunction, such as reduced heart rate variability (HRV), suggesting that disturbances in sympathetic–vagal regulation may contribute to the onset of symptoms and abnormalities in coronary vasodilation and vasoconstriction; moreover, there is considerable heterogeneity among patients [11,12]. At the same time, some patients may also present with abnormal pain perception, meaning that the severity of chest pain does not always correlate with the objective degree of myocardial ischaemia. It is therefore evident that the occurrence of MVA is not attributable to a single pathological mechanism, but rather results from the combined action of multiple factors, including structural changes in blood vessels, abnormal vascular reactivity, disturbances in neural regulation, and alterations in pain perception.

2.3 Diagnostic Criteria and Functional Classification

According to the COVADIS criteria [1], a definitive diagnosis of MVA requires the simultaneous presence of ischaemia-related symptoms, the absence of obstructive coronary artery disease, evidence of objective myocardial ischaemia, and evidence of impaired microvascular function [2,3]. In the presence of ischaemia-related symptoms and the absence of obstructive coronary artery disease, a diagnosis of suspected MVA may be considered if there is evidence of either objective myocardial ischaemia or coronary microvascular dysfunction. For patients with persistent symptoms that cannot be explained by routine anatomical investigations, modern guidelines emphasise further classification in conjunction with non-invasive myocardial perfusion/flow reserve assessment or invasive coronary functional testing [3,6] (See Table 1).

Table 1: COVADIS diagnostic framework for microvascular angina [1,2]

Elements	Key Points
Ischaemia-related symptoms	Exertional or resting chest pain, exertional dyspnoea, etc.
Non-obstructive CAD	Coronary stenosis <50% and/or FFR > 0.80
Objective evidence of ischaemia	Ischaemic ECG changes or stress imaging suggesting myocardial ischaemia
Microvascular dysfunction	Reduced CFR, increased microcirculatory resistance CUINX or acetylcholine-induced microvascular spasm

2.4 Modern medical treatment and its limitations

Treatment for MVA should include risk factor management, lifestyle interventions and anti-anginal therapy tailored to the specific pathological subtype. For patients with reduced CFR and/or elevated microcirculatory resistance, beta-blockers, calcium channel blockers, ACE inhibitors and reserpine may be considered as options for individualised treatment; for confirmed epicardial or microvascular spasm, calcium channel blockers are key therapeutic agents [2,3,13]. The main challenge with current Western medical treatment lies not in a lack of available drugs, but rather in the significant pathological phenotypic heterogeneity of MVA, the persistent disconnect between diagnosis and treatment, and the fact that some patients continue to experience symptoms even after receiving standard treatment. A recent systematic review, conducted using strict CMD functional diagnostic criteria, found that the number of existing studies on pharmacological treatment remains limited, and that there are discrepancies in the results regarding improvements in CFR and symptoms across different drugs, further supporting the necessity of individualised treatment based on pathophysiological subtypes [13]. Therefore, the management of MVA should place greater emphasis on mechanism-based stratification guided by coronary functional assessment, and individualised treatment strategies should be formulated according to specific pathophysiological subtypes.

3. Traditional Chinese Medicine's Understanding of MVA and Syndrome Differentiation and Treatment

3.1 Classification and Understanding of Pathogenesis

Traditional Chinese Medicine does not have a traditional term for 'microvascular angina'. Based on the primary manifestations such as chest pain, chest tightness, palpitations and shortness of breath, modern practitioners of Traditional Chinese Medicine generally classify it under categories such as 'chest bi' or 'heart pain'. Relevant TCM guidelines hold that the primary location of CMVD is the heart, with associations to the lungs, liver, spleen and kidneys; the nature of the disease is predominantly characterised by 'deficiency at the root and excess at the branch'. 'Deficiency at the root' may involve qi deficiency, yin deficiency or yang deficiency, whilst 'excess at the branch' commonly manifests as qi stagnation, blood stasis, phlegm-turbidity or cold-congestion; these may coexist and transform during the course of the disease [7,8].

3.2 Common Syndromes and Treatment Principles

Based on existing TCM diagnostic and therapeutic guidelines and consensus documents on integrated Chinese and Western medicine, clinical pattern differentiation is founded on the fluctuations in the abundance or deficiency of qi, blood, yin and yang, as well as pathological

factors such as phlegm, blood stasis and cold (Shown in Table 2).

Table 2: Common TCM syndromes and basic treatment methods summarised in CMVD-related guidelines [7-9]

Common Syndromes	Main Characteristics of the Syndrome (Summary)	Basic Treatment Methods
Qi Stagnation and Blood Stasis	Chest pain and chest tightness associated with emotional fluctuations; dark tongue or signs of stasis; string-like and rough pulse, etc.	Regulate qi and invigorate blood; unblock the meridians and relieve pain
Qi Deficiency with Blood Stasis	Recurrent chest pain, shortness of breath, fatigue and spontaneous sweating, accompanied by signs of blood stasis	Tonify qi and invigorate blood; unblock the vessels and relieve pain
Deficiency of both qi and yin	Chest pain or tightness, palpitations, shortness of breath, fatigue, dry mouth, etc.	Tonify qi and nourish yin; invigorate blood and unblock the meridians
Intertwined phlegm and blood stasis / Obstruction by turbid phlegm	Marked chest tightness, excessive phlegm or obesity, greasy tongue coating, accompanied by signs of blood stasis	Resolve phlegm and clear turbidity; invigorate blood and unblock the meridians
Cold stagnation in the heart meridians / Yang deficiency with cold stagnation	Symptoms are easily triggered or exacerbated by cold; aversion to cold and cold limbs; deep and slow pulse, etc.	Warming yang and dispelling cold; invigorating blood and unblocking the meridians

4. Clinical evidence for the integrated treatment of microvascular angina using traditional Chinese and Western medicine

MVA exhibits marked pathophysiological heterogeneity; different patients may present with impaired coronary microvascular dilation reserve, increased microcirculatory resistance, or microvascular spasm, and multiple abnormalities may coexist. Consequently, the therapeutic approach has gradually shifted from traditional empirical anti-anginal treatment towards individualised management based on coronary functional subtyping. The 2024 ESC Guidelines on Chronic Coronary Syndrome state that patients with ANOCA/INOCA should, in addition to lifestyle interventions and the management of cardiovascular risk factors, receive anti-anginal therapy selected according to their specific pathophysiological subtype [4]. Relevant expert consensus documents in China similarly emphasise the importance of assessing coronary microcirculatory function and implementing stratified treatment [6]. Within this diagnostic and therapeutic framework, Traditional Chinese Medicine (TCM) is better suited as a complementary intervention to standard modern medical diagnosis and basic treatment, in order to harness its potential advantages in symptom relief and holistic regulation; it should not replace modern medicine's functional stratification and basic treatment.

China has published the *Guidelines for the Integrated Traditional Chinese and Western Medicine Diagnosis and Treatment of Coronary Microvascular Disease* and related expert consensus documents, which have standardised the exploration of TCM pattern differentiation, compound herbal formulas and proprietary Chinese medicines in the treatment of CMVD [7,9]. It

should be noted that the research subjects covered by such guidelines and consensus documents often employ the relatively broad concept of CMVD, whilst some original studies also utilise previous diagnoses such as ‘cardiac X syndrome’; consequently, not all research findings can be directly equated with MVA diagnosed according to the current COVADIS criteria. On this basis, the evaluation of the therapeutic value of integrated Chinese and Western medicine should take into account the disease definition, the context of modern medical treatment, syndrome differentiation, and the quality of clinical research.

4.1 Overall Evidence on Combined Treatment with Traditional Chinese Medicine Formulations and Proprietary Chinese Medicines

Current clinical research on MVA in traditional Chinese medicine primarily compares ‘conventional Western medical treatment combined with Chinese herbal medicine or proprietary Chinese medicines’ with ‘conventional Western medical treatment alone’. Study outcomes include angina symptoms, exercise tolerance, electrocardiogram (ECG) findings, endothelial function indicators, inflammatory markers, and coronary microcirculation parameters such as CFR and IMR.

A systematic review conducted by Zhong et al. included a total of 24 randomised controlled trials involving 1,903 patients. The results indicated that the addition of blood-activating TCM to standard Western medical treatment may further improve angina symptoms, exercise test performance and certain endothelial function indicators, whilst also reducing high-sensitivity C-reactive protein (hs-CRP) levels. It should be noted, however, that this systematic review also pointed out that the included original studies had certain limitations in terms of randomisation, blinding and bias control, and that the overall methodological quality was low [14]. Therefore, although the current results suggest that Chinese herbal medicines for promoting blood circulation offer certain additional benefits, their clinical efficacy still needs to be verified through more rigorously designed, higher-quality studies.

Yu et al. conducted a meta-analysis incorporating 21 studies involving 1,641 patients with MVA. The results suggested that Chinese patent medicines combined with conventional treatment may improve indicators such as IMR, exercise treadmill duration, NO, ET-1 and hs-CRP; however, there was a degree of heterogeneity between studies, and the authors explicitly stated that further validation is required through higher-quality, randomised, double-blind clinical trials [15]).

Chen Jiaping et al. conducted a meta-analysis of randomised controlled trials evaluating oral Chinese patent medicines that tonify qi and activate blood circulation or dispel stasis for the treatment of coronary microvascular disease (CMVD), and assessed the quality of evidence using the GRADE system. The results suggest a trend towards improvement in some microcirculatory and clinical outcomes; however, the quality of evidence for key indicators such as the microcirculatory resistance index (IMR), coronary flow reserve (CFR) and high-sensitivity C-reactive protein (hs-CRP) was generally low, with most evidence rated as low or very low quality [16]. Building on this, a recent network meta-analysis further included 67 randomised controlled trials involving a total of 6,139 patients with CMVD, comparing the efficacy of 19 Chinese patent medicines in combination with standard treatment. The results showed that there were certain differences in the relative effects of different Chinese patent medicines on outcomes such as IMR, CFR, corrected TIMI frame count (cTFC) and endothelial function, providing a reference for the clinical selection of different formulations. However, due to factors such as the quality and heterogeneity of the included studies, the relevant ranking results still require further validation through more rigorously designed, higher-quality clinical trials [17].

4.2 Current Status of Clinical Research on Different Forms of Traditional Chinese Medicine Interventions

Currently, clinical practice involving TCM interventions for MVA/CMVD primarily encompasses two major categories: decoctions and proprietary Chinese medicines. Among these, formulations such as Tongxinluo Capsules, Qishen Yqi Drops, Shexiang Baixin Pills and Compound Danshen Drops have been widely utilised in numerous clinical studies and expert consensus documents [18]. Existing evidence suggests that various TCM formulations demonstrate potential clinical benefits in alleviating angina symptoms, enhancing exercise tolerance, and improving certain coronary microcirculatory parameters. Given the significant differences among formulations in terms of composition, indications, and intervention targets, clinical decision-making at this stage should place greater emphasis on individualised selection based on patients' specific clinical manifestations and TCM syndrome characteristics [7,9]. In terms of study design, Xie et al. conducted a double-centre, randomised, double-blind, placebo-controlled trial involving 80 patients with CMVD. The study aimed to evaluate the efficacy of Tongxin Fang as an intervention in addition to standard treatment, using coronary flow reserve (CFR) and the Seattle Angina Questionnaire (SAQ) as primary and secondary outcome measures [19]. This study clearly demonstrates that, in recent years, the research paradigm for the treatment of CMVD with traditional Chinese medicine has been gradually shifting from the traditional approach of evaluating efficacy based solely on symptoms to a comprehensive evaluation model that combines objective microcirculatory indicators with patient-reported outcomes. Another randomised controlled trial published in 2025 assessed the effects of Xinbao Pills in combination with standard treatment on SAQ scores, CFR and endothelial function-related indicators in patients with MVA, providing new empirical evidence for the clinical efficacy evaluation of proprietary Chinese medicines based on objective microcirculatory indicators [20].

The treatment of MVA with traditional Chinese medicine emphasises syndrome differentiation and treatment. Chinese guidelines on the integration of traditional and Western medicine, as well as relevant expert consensuses, have proposed corresponding treatment principles based on common syndromes such as qi deficiency with blood stasis and qi stagnation with blood stasis [7,9]. Against the backdrop of continuous advancements in modern coronary functional assessment, integrating the identification of TCM syndromes with the pathophysiological subtypes of MVA is expected to further enhance the precision of treatment. Clinical studies may conduct syndrome stratification based on a confirmed diagnosis of MVA and the status of microcirculatory function, and compare differences in the efficacy of TCM interventions among patients with different syndromes, thereby exploring the relationship between 'disease subtype—TCM syndrome—treatment regimen'.

Some previous studies in traditional Chinese medicine have employed diagnostic concepts such as 'cardiac X syndrome'; these early explorations have accumulated valuable clinical data for understanding the efficacy of traditional Chinese medicine in alleviating chest pain associated with non-obstructive coronary artery disease (ANOCA/INOCA). With the establishment of the COVADIS diagnostic criteria and the widespread adoption of functional indicators such as coronary flow reserve (CFR) and the microcirculatory resistance index (IMR), the research evaluation framework in this field has, in recent years, been gradually shifting from a focus solely on the improvement of clinical symptoms and the assessment of efficacy via electrocardiogram (ECG) to a multidimensional approach incorporating objective microcirculatory function indicators, patient-reported outcomes (PROs) and quality of life. Looking ahead, if high-quality, standardised clinical trials are conducted based on unified modern medical diagnostic criteria and TCM syndrome classification, it is expected that the target patient populations for different Chinese herbal preparations in MVA patients can be defined more precisely, and high-level evidence-based

medical evidence can be provided to support their clinical benefits.

4.3 Acupuncture and Comprehensive Non-pharmacological Interventions

In addition to treatment with Chinese herbal medicines, acupuncture, emotional regulation and exercise rehabilitation have a certain foundation of application in the management of chest pain and chronic cardiovascular diseases; however, high-quality clinical evidence specifically targeting patients with MVA who have been definitively diagnosed via modern coronary functional testing remains limited. Relevant Chinese guidelines and expert consensuses regard lifestyle modifications, exercise rehabilitation and comprehensive management as integral components of CMVD treatment [3,6]. With regard to acupuncture, the current evidence largely originates from other patients with ischaemic heart disease or basic laboratory studies; consequently, it is not yet possible to conclude that acupuncture can improve CFR or reduce IMR in patients with MVA. Recently, a protocol for a randomised, sham-acupuncture-controlled exploratory trial targeting INOCA-related CMVD has been published, and evaluation systems have begun to incorporate the SAQ, quality of life, and endothelial and inflammation-related indicators, reflecting that acupuncture research is gradually moving towards standardised diagnosis, placebo-controlled trials, and patient-reported outcomes [21].

Patients with MVA often experience recurrent symptoms, as well as psychosocial issues such as the cognitive burden of the condition and anxiety and depression; psychological stress itself can induce or exacerbate coronary vasomotor dysfunction. Against this backdrop, an integrated Chinese and Western medicine management model should incorporate comprehensive interventions—including psychological screening, sleep management, patient education and exercise rehabilitation—into the overall treatment framework. However, it must be clarified that psychological factors are one of the key variables that may influence MVA symptoms and vascular reactivity, rather than the sole cause of chest pain in all patients. For patients with a confirmed diagnosis of CMD, even if they also suffer from anxiety or depression, their ischaemic symptoms should not be simplistically attributed to ‘psychogenic chest pain’, so as not to obscure underlying microcirculatory dysfunction.

4.4 Evaluation of the Efficacy of Integrated Traditional Chinese and Western Medicine Treatment

When assessing the clinical value of integrated traditional Chinese and Western medicine (TCM-WM) for the treatment of MVA, one should not be limited to traditional indicators such as the ‘overall response rate’ or improvements in electrocardiogram (ECG) findings; rather, a comprehensive evaluation of patients’ symptomatic benefits, coronary microcirculatory function indicators, quality of life and safety is required. However, there is significant heterogeneity in the selection of outcome measures in current relevant studies. Zhang and colleagues conducted a systematic review of 69 randomised controlled trials on the treatment of MVA with traditional Chinese medicine, identifying a total of 100 outcome measures covering multiple dimensions, including clinical efficacy, symptoms and signs, laboratory and auxiliary examinations, TCM syndromes, safety and quality of life. This study revealed that existing research generally suffers from issues such as a large number of indicators, inconsistent definitions and measurement methods, and a lack of long-term follow-up endpoints [22].

Consequently, future clinical research on integrated Chinese and Western medicine should establish a multidimensional evaluation system comprising patient-reported outcomes, coronary microcirculatory function and safety. At the symptomatic level, the frequency and duration of angina attacks should be recorded, utilising scales such as the SAQ; at the microcirculatory level,

priority should be given to objective indicators such as CFR, IMR and quantitative myocardial blood flow reserve [4].

4.5 Current Positioning of Integrated Traditional Chinese and Western Medicine Treatment

Based on current evidence-based medical evidence, the current role of traditional Chinese medicine in the treatment of MVA should be clearly defined as an adjunctive intervention strategy built upon standardised modern medical diagnosis and treatment. Its core potential value is primarily reflected in the alleviation of angina symptoms, the enhancement of patients' quality of life, and the improvement of certain microcirculatory and endothelial function indicators [14-20]. However, existing studies still exhibit significant heterogeneity in terms of diagnostic criteria, study populations and the selection of outcome measures, and there is a general lack of high-quality evidence-based data assessing long-term cardiovascular prognosis [14-17].

5. Research on Modern Pharmacological Mechanisms: A Perspective Combining Traditional Chinese and Western Medicine

The onset and progression of microvascular angina (MVA) involve multiple pathological mechanisms, including microvascular endothelial dysfunction, oxidative stress, inflammatory responses, and microvascular structural remodelling [4,10]. Compound traditional Chinese medicines and their active constituents possess pharmacological characteristics characterised by multiple components and multiple targets; theoretically, they may act simultaneously on several of the aforementioned mechanisms, providing a research foundation for explaining the intervention of traditional Chinese medicine in MVA from a modern pharmacological perspective.

5.1 Improvement of vascular endothelial function: modulation of the eNOS/NO signalling pathway

Coronary microvascular endothelial cells participate in the regulation of coronary blood flow by releasing vasoactive substances such as nitric oxide (NO), prostacyclin and endothelin. Among these, NO generated by endothelial nitric oxide synthase (eNOS) is a key mediator in maintaining the vasodilatory response. Endothelial dysfunction can lead to reduced NO bioavailability and a relative increase in the action of vasoconstrictor mediators, thereby limiting the vasodilatory capacity of microvessels when myocardial oxygen demand increases; this is one of the key pathological mechanisms underlying functional CMD [4,10].

The biological activity of eNOS does not depend solely on its protein expression level, but is finely regulated by multiple factors, including phosphorylation, enzyme-substrate coupling efficiency, and the cellular redox microenvironment. Therefore, when evaluating the endothelial protective effects of traditional Chinese medicine, it should not be simply attributed to 'upregulation of eNOS expression', but should be systematically assessed from multiple dimensions, including eNOS phosphorylation and activation, NO biosynthesis, and endothelial-dependent vasodilation.

Puerarin is one of the major isoflavone components of Pueraria root. Hwang et al. found in cultured endothelial cells that puerarin promotes phosphorylation at the eNOS Ser1177 site and NO production, with its action involving oestrogen receptor-dependent PI3K/Akt and CaMKII/AMPK-related signalling; simultaneously, it inhibits TNF- α -induced NF- κ B activation and inflammatory responses in endothelial cells [23].

Tanshinone IIA is a well-studied lipophilic bioactive component of *Salvia miltiorrhiza*. In vitro vascular studies by Fan et al. demonstrated that tanshinone IIA promotes eNOS activation and NO production via oestrogen receptor-related non-genomic signalling, thereby producing an

endothelium-dependent vasodilatory effect [24]. Li et al. further observed in streptozotocin-induced diabetic rats and human umbilical vein endothelial cells treated with high glucose that tanshinone IIA can improve the diabetes-related decline in endothelium-dependent vasodilation and regulate eNOS expression, phosphorylation and NO production [25].

The endothelial protective effects of ginsenosides have also attracted attention. Hien et al. found that ginsenoside Rg3 increases eNOS phosphorylation and expression in cultured endothelial cells and promotes NO production via oestrogen receptor-dependent PI3K/Akt and AMPK-related signalling pathways [26]. This suggests that ginsenoside Rg3 may contribute to vascular protection by enhancing the endothelial capacity for NO production.

5.2 Anti-inflammatory and Antioxidant Effects: Intervening in the Mutual Amplification of Inflammation and Oxidative Stress

Oxidative stress and low-grade inflammation are key factors in the onset and progression of CMD. Excessive production of reactive oxygen species (ROS) can directly damage the vascular endothelium whilst reducing the bioavailability of NO; oxidative stress can also activate inflammation-related signalling pathways such as NF- κ B, promoting the expression of inflammatory mediators. Conversely, inflammatory cells and mediators can further increase ROS production via NADPH oxidase and mitochondrial dysfunction, thereby forming a pathological process in which inflammation and oxidative stress mutually reinforce each other [10]. This process may further exacerbate endothelial dysfunction and may contribute to long-term structural changes in microvessels.

The antioxidant effects of traditional Chinese medicine should not be understood merely as the direct ‘scavenging of free radicals’; their mechanisms may also involve reducing ROS production, regulating NADPH oxidase, improving the endogenous antioxidant system, and inhibiting inflammatory signalling. Tongxinluo is one of the compound formulations that has been relatively extensively studied at the level of cardiac microvascular endothelial cells. Wu et al. found, in human cardiac microvascular endothelial cells and in an atherosclerosis model using ApoE-deficient mice, that following Tongxinluo intervention, oxidative stress markers such as ROS and malondialdehyde (MDA) were reduced, whilst NF- κ B-related inflammatory responses were suppressed, accompanied by improved expression of endothelial-associated proteins such as CD31 and eNOS [27].

Wang et al., using an hypoxia model involving co-culture of macrophages and human cardiac microvascular endothelial cells, found that macrophages can exacerbate peroxynitrite-induced microvascular endothelial cell damage, whilst Tongxinluo intervention reduces the accumulation of nitrotyrosine and alleviates endothelial damage, whilst also influencing the expression of relevant molecules such as iNOS, endothelin-converting enzyme, COX-2 and prostacyclin synthase [28].

Compared with basic research, clinical evidence of inflammation in patients with MVA should be interpreted with greater caution. A meta-analysis by Zhong et al. showed that hs-CRP levels may decrease following the combination of blood-activating Chinese herbal medicines with conventional treatment; however, the combined results for TNF- α and IL-6 did not reach statistical significance [14].

5.3 Anti-fibrosis and microvascular structural remodelling: evidence for indirect mechanisms

In addition to dynamic vasomotor dysfunction, some patients with CMD also present with structural microcirculatory abnormalities, the main pathological manifestations of which include microarterial wall thickening, luminal remodelling, reduced capillary density and perivascular fibrosis. These structural changes can significantly increase minimum microvascular resistance, limiting the increase in coronary blood flow perfusion during hyperaemia, thereby leading to

reduced CFR or increased microcirculatory resistance [4,10]. Consequently, inhibiting myocardial fibrosis and abnormal vascular remodelling may represent important intervention targets for the long-term improvement of structural CMD.

A body of basic experimental data has been accumulated regarding the role of traditional Chinese medicine in combating myocardial fibrosis, modulating the extracellular matrix, and regulating the endothelial-mesenchymal transition; however, research specifically targeting microvascular structural remodelling in MVA remains markedly insufficient. Jin et al. found in models of pressure-overloaded mice and human umbilical vein endothelial cells that puerarin alleviates myocardial fibrosis, inhibits endothelial-mesenchymal transition, and downregulates TGF- β 1/Smad2-related signalling, accompanied by upregulation of PPAR- γ expression [29].

Recently, research by Ge and colleagues has provided key experimental evidence for the use of traditional Chinese medicine formulations in the management of CMD. By establishing a CMD rat model and a cardiac microvascular endothelial cell model, this study confirmed that the ‘Regulating Qi, Resolving Phlegm and Activating Blood Circulation’ formula can reduce collagen deposition in myocardial tissue, inhibit inflammatory responses and cell apoptosis, and improve mitochondrial function in microvascular endothelial cells; its mechanism of action may be related to the regulation of the NRG-1/PI3K/AKT signalling pathway [30]. Compared with traditional models of stress loading or myocardial fibrosis, this study directly utilised a CMD model, thereby providing experimental evidence with greater pathophysiological relevance for TCM interventions targeting structural and functional abnormalities of the microcirculation.

5.4 Integrated Understanding of the Multi-Target Effects of Traditional Chinese Medicine and the Construction of a Chain of Evidence

A solid body of experimental evidence has been accumulated regarding the effects of TCM and its active constituents on pathological processes such as endothelial protection, inflammation, oxidative stress and fibrosis, whilst autonomic dysfunction is increasingly emerging as a potential intervention target worthy of in-depth exploration. Among these, research evidence targeting the eNOS/NO pathway is relatively concentrated and the mechanism is fairly well established: tanshinone IIA, puerarin and ginsenoside Rg3 have all been validated in cellular or animal experiments [23-26]. Tongxinluo Capsules have also been shown to exert antioxidant, anti-inflammatory and endothelial protective effects in human cardiac microvascular endothelial cells [27,28]. Furthermore, the modulation of TGF- β 1/Smad2-related fibrotic signalling by puerarin provides experimental evidence for the intervention of structural vascular remodelling [29]. At the clinical research level, several systematic reviews and meta-analyses have also observed that certain traditional Chinese medicine interventions can influence markers such as NO, ET-1, hs-CRP, CFR or IMR [14-17]. The aforementioned basic and clinical evidence collectively suggests that traditional Chinese medicine may intervene in the complex pathophysiological network of MVA through multi-stage, multi-target mechanisms.

Furthermore, autonomic dysfunction is also thought to be involved in the pathophysiological processes of some MVA patients. However, there is currently a lack of direct experimental or clinical evidence demonstrating that TCM interventions can modulate autonomic function and thereby further improve coronary microcirculation. Consequently, this area remains a potential intervention strategy in urgent need of exploration and represents an important avenue for future research.

6. Current Issues and Future Research Directions

6.1 Standardisation of Study Subjects and Diagnostic Subtypes

Previous research on traditional Chinese medicine has often used ‘cardiac X syndrome’, ‘coronary angiographically normal angina’ or ‘CMVD’ as inclusion criteria, resulting in heterogeneity within the study population. In future, priority should be given to adopting the COVADIS criteria or the latest guideline standards to clarify the pathophysiological subtypes of MVA, such as impaired microvascular dilation, increased microcirculatory resistance or microvascular spasm, and to differentiate these from other ANOCA/INOCA subtypes, such as epicardial vasospasm, whilst reporting key data such as CFR, IMR, FFR and the acetylcholine test [1-3,31].

6.2 Improving the reproducibility of Traditional Chinese Medicine (TCM) syndromes

Traditional Chinese Medicine (TCM) syndromes should be assessed in accordance with standardised guidelines and quantification tools; reports should detail the composition of syndromes, the training of practitioners conducting syndrome differentiation, and consistency evaluations. Further exploration of statistical associations between syndromes and CFR, IMR, inflammation, metabolomics or autonomic nervous system indicators may be undertaken; however, these must be validated through independent cohorts to avoid establishing a fixed ‘one syndrome, one indicator’ correspondence *a priori*.

6.3 Optimising Clinical Trial Design and Core Outcomes

Future trials should improve the quality of randomisation sequences, allocation concealment, blinding, registration and protocol transparency; for proprietary Chinese patent medicines, placebo-controlled designs should be adopted wherever possible, whilst for decoctions, bias must be minimised through independent outcome assessment. For primary endpoints, patient-reported outcomes such as the SAQ and frequency of angina attacks should be prioritised; objective microcirculatory indicators—such as invasive CFR, IMR, and myocardial flow reserve (MFR) as measured by PET or quantitative CMR—should be adopted according to the study conditions. Long-term prognostic outcomes, such as MACE, can only be reasonably evaluated when sample size and follow-up duration are sufficient.

6.4 Establishing a chain of evidence from the chemical basis to the clinical phenotype

Research into the mechanisms of compound preparations should first clarify quality control, *in vivo* exposure to active ingredients and their metabolites; then establish causal relationships through cellular, animal and target-specific validation; and finally verify whether corresponding functional indicators are improved in patients with clearly defined MVA phenotypes. Only in this way can the sequence ‘active ingredient – molecular pathway – microcirculatory function – clinical symptoms’ be linked into a verifiable chain of evidence.

7. Conclusion

As a heterogeneous ischaemic syndrome characterised by structural and functional abnormalities of the coronary microvasculature, the diagnostic and therapeutic paradigm for MVA has gradually shifted from ‘empirical management following the exclusion of obstructive coronary heart disease’

towards stratified management based on pathophysiological phenotypes, guided by coronary functional assessment. Current evidence suggests that combining certain traditional Chinese medicines or proprietary Chinese medicinal preparations with conventional treatment can, to a certain extent, improve patients' angina symptoms and certain microcirculatory, endothelial function and inflammatory markers; however, due to the heterogeneity of study designs and inconsistencies in outcome measures, the overall quality of the existing evidence still needs to be improved. Although a certain body of basic research evidence has been accumulated regarding Danshenone IIA, puerarin, ginsenosides and certain TCM formulations in relation to targets such as the eNOS/NO pathway, inflammation-oxidative stress and fibrosis, academic evaluation must still carefully distinguish between the conclusions of experimental studies and the mechanisms of clinical efficacy, avoiding the direct equating of findings at the cellular or animal level with benefits in humans. Looking ahead, the key breakthrough in integrated Chinese and Western medicine research lies in: unifying the MVA diagnosis of endotypes with Traditional Chinese Medicine (TCM) syndrome classification; adopting objective, quantifiable microcirculatory functional endpoints; and rigorously improving the methodological quality of randomised controlled trials. Only in this way can we precisely determine which TCM interventions can provide verifiable, clinically significant benefits to which patient groups.

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