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Related factors of coronary no-reflow phenomenon and progress of traditional Chinese medicine treatment

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ABSTRACT

Coronary no-reflow phenomenon belongs to a type of coronary microcirculation disturbance, and its main pathogenic factors are vascular endothelial cell injury, microembolism and inflammatory reaction, which are corresponding to the pathogenesis of choroid injury, blood stasis and heat toxin in traditional Chinese medicine, such as NO, ET-1, chemokine, IL and other cytokines. The degree of improvement of patients' symptoms and laboratory examination data provide a basis for traditional Chinese medicine compound prescription, monomer and traditional Chinese medicine characteristic therapy for the treatment of no-reflow phenomena (NRP). Combined with related factors, the author summarizes the research progress of traditional Chinese medicine treatment of NRP in recent years, in order to provide clinical reference.

1. Introduction

The phenomenon of no reflow of coronary artery refers to the phenomenon that myocardial perfusion is still insufficient after epicardial coronary artery occlusion is opened and other vascular obstruction is excluded (thrombus, dissection, spasm, dissection, *etc*.)[1]. NRP is an important phenotype of coronary microcirculatory disturbance,which is often seen after mechanical treatment of obstructive vessels (balloon dilatation, stent implantation, *etc*.). It is a serious complication of percutaneous coronary intervention. The main clinical manifestations are recurrent chest tightness (or pain), dyspnea, and cardiac death. The incidence of NRP in patients with acute myocardial infarction after emergency PCI can reach 60%[2], and NRP is an independent predictor of recurrent myocardial infarction after PCI[3]. In 2016, Niccoli et al. summarized five mechanisms of NRP (ischemic injury, reperfusion injury, microvascular dysfunction (MVO), distal microthromboembolism, individual susceptibility)[4], among which vascular endothelial cell injury, inflammatory reaction and distal microembolism are the main factors,but the specific molecular mechanism is not clear. Traditional Chinese medicine plays a role with multiple pathways and targets, and has the advantages of high safety and low side effects. Combined with relevant factors, this paper summarizes the mechanism of traditional Chinese medicine in the treatment of NRP.

2. Understanding of NRP in traditional Chinese medicine

There is no special record of NRP in traditional Chinese medicine.according to the clinical characteristics, NRP should belong to the category of "chest arthralgia", "heartache", "long heartache" and so on. The typical manifestations of "chest pain" are chest pain (or tightness), shortness of breath, shortness of breath, wheezing, *etc*., such as "plain question": "Heart disease, chest pain, full side support…" "Pain in both arms." Various sources of diseases on heartache disease princes said: "those with long heartache are different collaterals of the heart, which is also caused by the cold and heat of wind evil." It clarifies that the disease of long heartache is located in the heart collaterals, which is caused by the multiplication of poison and evil. It is consistent with chest pain, shortness of breath and other symptoms in

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patients with NRP. In terms of anatomical structure and function, the Sun collaterals of the TCM choroid system contains the coronary microvessels on the surface of the heart,and the network and dispersion of the heart Sun collaterals structure are consistent with the network structure and diffusion of coronary microvessels. Both have the role of nutrition and energy metabolism[5].

3. The mechanism of no reflow treated by traditional Chinese medicine

3.1 Effect of choroid injury on EC of NRP microvessels

Based on anatomy, TCM qi and blood theory and western medicine analysis techniques, the study of "Sun Luo-microvascular" pathological changes included four pathological types: sun Luo deficiency acute-microvascular contraction; Sun Luo neglect-decrease in the number of microvessels; Sun Luo breeding-abnormal microvascular growth; Sun Luo stasis-microvascular embolism,all accompanied with hemorheological abnormalities. The core and initiating factor of "Sun Luo-microvascular" lesion is that microvascular EC, nerve, body fluid and blood are involved,and many complex causes cause organic damage[6]. The theoretical system focuses on microvascular EC, to provide ideas for the study of NRP.

3.1.1 Mechanism of NRP microvascular EC and cardiomyocyte injury

In 1974, Kloner *et al*.[7] ligated the coronary artery of dogs for 90 minutes to make an animal model of ischemia/reperfusion (IR). It was found that the ischemic microvascular EC showed morphological changes such as swelling and protruding; the enlargement of EC space and extravascular exosmosis increased extravascular pressure; swollen cells and extravascular pressure acted on the microvessels together to narrow the lumen. Persistent ischemia and hypoxia inhibit the Na^+/K^+ pump in the myocardium, abnormal entry and exit of Ca^{2+}, accumulate in the cells,resulting in calcium overload, resulting in excessive contraction of myocardial fibrous cells and compression of blood vessels[8]. In the myocardium after IR, a large number of monocytes gather and differentiate into criminal macrophages, which may produce large amounts of reactive oxygen species through the MKL1-MOF-NOX axis; in addition, excessive intracellular Ca^{2+} activating xanthine oxidase (XO), can also promote the formation of reactive oxygen species clusters, these strong oxidants can destroy the function of mitochondria by being absorbed by mitochondria, on the other hand, they can act on EC, to activate the coagulation system and promote thrombus[9-12]. Ma Xuekuan *et al*.[13] conducted animal experiments with the traditional Chinese medicine compound Tianxiangdan (Rhodiola: Salvia miltiorrhiza: Xintahua: Jiangxiang=8:8:6:3). It was found that compared with nicorandil group[14,15], which has been proved to be effective against mitochondrial injury and ischemia, the expression of nuclear transcription factor E2 related factor 2 (Nrf2) in myocardium of rats in Tianxiangdan group was higher than that in nicorandil group[14,15]. Nrf2 forms Nrf2/ARE signal pathway with antioxidant response element(ARE), which plays the role of antioxidation and reduces myocardial stress injury.

3.1.2 Nitric oxide (NO)

NO is a signal molecule that exists widely in myocardial tissue. After microvascular EC damage in NRP, on the one hand, vascular structural changes lead to lumen stenosis, on the other hand, it directly reduces the production of endothelium-dependent NO. Some experimental studies have confirmed that there is a correlation between NO content and myocardial injury in the process of myocardial ischemia[16]. The role of NO in NRP is mainly manifested in two aspects,one is as a vasodilation factor to reduce intravascular pressure, play a relaxing role, and maintain myocardial blood perfusion[17]; the other is to act on mitochondrial ATP sensitive K^+ channels and related enzymes, reduce mitochondrial membrane permeability, reduce tissue reactive oxygen species content, inhibit Ca^{2+} overload, and play an antioxidant role[18]. In addition,some studies have shown that NO can play an anti-inflammatory effect by reducing the adhesion of inflammatory cells[19]. YING *et al*.[20] confirmed that compound Danshen tablet (prescription: Salvia miltiorrhiza, borneol, Panax notoginseng) can significantly increase the expression of NO rate-limiting enzyme-NOS in IR rats, promote the production of NO, protect damaged cardiomyocytes and reduce the area of myocardial infarction in rats.

3.1.3 The vasodilating effect of endothelin-1 (ET-1)

ET-1 is opposite to that of NO, it is a bioactive peptide secreted by EC and has strong vasoconstrictive effect. Animal experiments showed that ET-1 in myocardial tissue related to NRP increased significantly in rabbits, which may be due to the synthesis and secretion of a large amount of ET-1, after vascular EC stimulation, but the accumulation of ET-1 was caused by the disturbance of coronary microcirculation and blood flow ET-1 is a bioactive peptide secreted by EC and has strong vasoconstrictive effect. Animal experiments showed that ET-1 in myocardial tissue related to NRP increased significantly in rabbits, which may be due to the synthesis and secretion of a large amount of ET-1, after vascular EC stimulation, but the accumulation of ET-1 was caused by coronary microcirculation disturbance and blood flow obstruction[21]. Strong vasoconstriction leads to microvasospasm,which further aggravates the disturbance of coronary microcirculation. In the pathological state of NRP,the structure of vascular EC is damaged and endothelial dysfunction occurs, which reduces the synthesis and utilization of NO, while the local tissue ET-1 increases, which breaks the balance between NO and ET-1, and destroys the vasomotor function of blood vessels[22]. Clinical trials and pharmacological studies show that Shenmai injection and breviscapine injection can significantly reduce the level of ET-1, promote the synthesis and release of NO, inhibit vasoconstriction and improve endothelial function[23]. Lin Xiaoyuan *et al*.[24] the rat model of endothelial dysfunction complicated with hypertension was made with NOS inhibitor and treated with compound Gouteng Jiangya tablet. It was found that the drug could promote the expression of eNOS, reduce serum ET-1, improve the imbalance of NO and ET-1, and reduce the pressure in the lumen.

3.2 Correlation between NRP and blood stasis

"Shuo Wen Jie Zi" said: "Blood stasis accumulates blood. "Wang Qingren said in "Yilin correcting mistakes" that "if the blood is cold,it condenses into a lump" and "if the blood is heated,it is boiled into a lump". In the blood circulation, changes in the internal and external environment of the body can lead to abnormal operation of qi and blood and form blood stasis. Blood stasis obstructs the heart pulse, clinical often have chest pain such as thorn, pain has fixed place, tongue purple dark ecchymosis, sublingual venation circuitous and other symptoms. Microvascular embolism is an important pathological basis of NRP, except for intuitive mechanical embolism such as exfoliated plaque and thrombus, and the biological effects of various factors promoting thrombosis produced by vascular endothelium stimulation should not be underestimated, both of which belong to the category of blood stasis in traditional Chinese medicine.

3.2.1 Thromboxane A2 (TXA2) and prostacyclin I2 (PGI2)

Thromboxane A2 (TXA2) and prostacyclin I2(PGI2)are synthesized by vascular EC, and under physiological condition, they can be in dynamic equilibrium; when NRP occurs, cell membrane phospholipase A2 is activated by pro-inflammatory factors secreted by leukocytes, arachidonic acid on the membrane is oxidized and decomposed, and TXA2/PGI2 balance is out of balance, which reacts on EC. The study shows that the increase of Tamp P ratio is more likely to play a destructive role than a single numerical change[25]. TXA2 and PGI2 activate the TP receptor and IP receptor of endothelium and platelet, respectively. The former can induce vasoconstriction and platelet aggregation, while the latter is vice versa[26]. Cao Chunshui *et al*.[27] animal experiments confirmed that tanshinone can promote the release of PGI2 and inhibit the synthesis of TXA2.Many studies[28–30] show that Xuesaitong dispersible tablets, which is mainly composed of Panax notoginseng saponins, can effectively reduce the content of serum TXA2, improve vascular endothelial function, reduce blood viscosity and improve microcirculation.

3.2.2 Vascular endothelial growth factor (VEGF)

There are a wide range of neovascularization in human atherosclerotic plaque. Different from ordinary blood vessels, it has no complete vascular structure and has the characteristics of brittleness and easy to rupture[31,32]. The risk of plaque neovascularization is mainly manifested in three aspects: one is to promote inflammation; the second is to provide nutrition for plaque and promote the process of atherosclerosis; third, it is easy to bleed, increase the risk of plaque rupture and promote thrombosis[33–36]. VEGF is an important target gene of neovascularization. When NRP occurs, the coronary artery is in a state of ischemia and hypoxia for a certain period of time. This pathological environment can increase the activity of hypoxia-induced transcription factor(HIF-1 α) and promote the expression of VEGF[37]. Some studies have also shown that chemokine receptor 4 (CXCR4) is closely related to VEGF, and the former may promote angiogenesis in plaques by up-regulating the expression of VEGF[38]. Wumishan *et al*.[39] showed that Xu Shaohuo capsule (prescription: aconite, Panax quinquefolium, Acorus calamus, Salvia miltiorrhiza, Fructus Aurantii, Platycodon grandiflorum, Pueraria lobata, Glycyrrhiza uralensis, *etc*.), simvastatin and Tongxinluo capsule could significantly reduce the expression of VEGF, maintain plaque stability, slow down the process of atherosclerosis and protect vascular endothelium.

3.3 Correlation between NRP and heat toxin

"Shuo Wen Jie Zi" said: "poison, thick also, harmful grass. "From the beginning of Nei Jing,there have been records of "heat and poison" leading to "heart disease". Ding Shuwen, a famous veteran traditional Chinese medicine doctor, established the heat-toxin theory system of heart diseases,and benefited a lot from the treatment of heart diseases with the method of invigorating qi, removing blood stasis and detoxification[40]. After PCI, local blood vessels show inflammation, edema, redness, swelling, heat, pain and other pathological changes, which is called "heat toxin" in traditional Chinese medicine. The pathological changes such as inflammatory reaction, oxidative stress, tissue necrosis and autophagy, and thrombus organization in the process of plaque and thrombosis in NRP are the result of the joint action of "blood stasis" and "poison".

3.3.1 Vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1)

Inflammatory reaction is accompanied by the occurrence and development of NRP, and the adhesion between leukocytes and vascular EC is the key to inflammatory reaction. Although criminal blood vessels have been opened, long-term myocardial ischemia makes polymorphonuclear neutrophils (PMN), which is larger and harder than red blood cells, to form activated cells with less deformability, and a large number of white blood cells converge and block in microvessels, which on the one hand cause microcirculation disturbance, on the other hand, make local inflammatory reaction. The above-mentioned effects of PMN need to be mediated by representative immunoglobulin molecules such as VCAM-1 and ICAM-1. Both VCAM-1 and ICAM-1 exist in vascular endothelium, and VCAM-1 can mediate the adhesion between T cells,monocytes, eosinophils and EC except PMN. ICAM-1 is the ligand of PMNCD18, which mainly mediates the adhesion of PMN to EC after reperfusion injury, and participates in the transfer of PMN across vascular EC to myocardial tissue[41–43]. Cell experiments show that[44] Astragalus polysaccharides, a monomer component of traditional Chinese medicine, can significantly reduce the contents of VCAM-1 and ICAM-1, and play the role of anti-inflammation and anti-embolism.

3.3.2 CXC chemokine

Chemokines are a kind of small molecular secretory proteins,which can induce inflammatory cell chemotaxis and play an important role in inflammatory response by binding to corresponding receptors. In the process of myocardial IR injury, EC, CXC chemokine and adhesion molecules play an important role from the initial migration and adhesion of leukocytes to the final passage of vascular chemokines and adhesion molecules. Some studies have shown that compared with TNF- α and ICAM-1, CXCL16 reaction and the time to reach the peak, it can promote leukocyte migration earlier and faster[45,46]. Specifically, CXCL16 stimulates T lymphocytes to release factors

such as interferon-γ and TNF-2-β,which destroys the function of surrounding cells, while interferon-γ further stimulates the expression of CXCL16mRNA[47,48]. In arterial diseases, CXCR2, the main receptor of CXCL1, promotes inflammation by promoting monocyte aggregation and infiltration,and the use of CXCR2 inhibitors can significantly inhibit plaque formation[49]. Studies have shown that Salvianolic acid A (SAA) can reduce inflammation by inhibiting the secretion of CXCL1 and CXCL2, and inhibit platelet and PMN activation and aggregation by inhibiting complement C3aR. Salvianolic acid has significant anti-myocardial ischemia and anti-inflammatory effects[50].

3.3.3 Interleukin-(IL)

Interleukin-(IL) is an inflammatory factor that can participate in the inflammatory response of various tissues and organs of the whole body.Among them,the pro-inflammatory factors IL-1β, IL-6, IL-17A and anti-inflammatory factor IL-10 are closely related to NRP. At present,there are mainly pro-inflammatory factors,IL-6,IL-17A and anti-inflammatory factors.IL-1β is the main subtype of IL-1, which comes from the inflammatory bodies of NLRP3. It can induce the expression of adhesion molecules, promote perivascular inflammation and migrate and infiltrate the myocardial tissue[51]. Some studies have shown that IL-1β is positively correlated with cathepsin S (CatS), while CatS can degrade insoluble elastin and destroy plaque stability[52]. IL-6 is mainly secreted by macrophages and monocytes. IL-6 has two main functions in NRP: one is to directly damage blood vessels and EC, to recruit other inflammatory factors to promote inflammation, and the other is to accelerate the process of plaque, thrombus and myocardial remodeling[53,54]. IL-17A mainly comes from $CD4^+$T cells. Recent studies have paid attention to its role in myocardial immunity and inflammation after Imax R[55]. it has been found that PI3K/Akt pathway is a possible way for IL-17A to affect cardiomyocyte apoptosis, which can expand the area of myocardial infarction and destroy myocardial function[56]. IL-10 is an anti-inflammatory factor mainly secreted by Th1, Th2 cells and macrophages[57-59]. Rennick et al. found that the expression of TNF-α and ICAM-1 was significantly up-regulated in IL-10-deficient mice in myocardial IR injury[60]. Related studies have shown that IL-10 can not only inhibit inflammation by reducing the expression of TNF-α, IL-6, IL-8, IL-1 and other inflammatory factors, but also inhibit the abnormal proliferation of vascular smooth muscle caused by inflammatory factors and chemokines, and protect myocardial tissue[61].

Since Zhongjing, the pathogenesis of "Yang Weiyin string" in patients with chest paralysis has been widely recognized. Some studies have shown that Qishen Yiqi dripping pills composed of Radix Astragali, Radix Notoginseng, Radix Notoginseng, Radix Salviae Miltiorrhizae, Radix Salviae Miltiorrhizae and Radix Salviae Miltiorrhizae, which is composed of tonifying blood stasis and activating blood circulation, can make deficiency yang warm and Yu Bi tong[62], which can reduce the contents of serum NT-proBNP, TNF-α, CRP and IL-6, and increase IL-10, to play the effects of anti-inflammation, cardiotonic and antithrombotic[63]. Modern pharmacological studies have confirmed that safflower has the function of anti-platelet aggregation and vasodilation, and Salvia miltiorrhiza can reduce blood flow resistance, inhibit oxygen free radicals and Ca^{2+} influx[64]. The compound Danhong injection composed of two can significantly reduce the serum inflammatory indexes such as IL-6, Cys-C, Hcy and improve the disturbance of coronary circulation in NRP mice[65,66]. High mobility group protein B1 (HMGB1) promotes the secretion of IL-17 by inducing IL-23 to act on Thl7 cells,while tanshinone IIA can reduce the expression of HMGB1 and IL-23/IL-17 axis in NRP region, thus reducing inflammation and myocardial injury[67]. In addition, some studies said that after treatment with electroacupuncture at"Neiguan"+"Xinshu", the content of serum IL-1β in the electroacupuncture group was (42.15 ±7.95) ng/L, lower than that in the"Taiyuan"+"Feishu" group (70.38 ±12.59) ng/L,and lower than that in the model group (80.87 ±10.25) ng/L.The content of anti-inflammatory factor IL-10 (77.25 ±7.88) ng/L was higher than that of "Taiyuan"+"Feishu" group (63.09 ±6.13) ng/L, and higher than that of the model group (58.67 ±6.41) ng/L, ischemic area NF-κ Bp65 protein content also significantly decreased, indicating that "Neiguan" + "Xinshu" group can play the role of anti-inflammation, anti-ischemia and infarction through NF-κ B signal pathway[68]. The above clinical and animal experiments show that traditional Chinese medicine can regulate related inflammatory factors to inhibit inflammatory response and protect related blood vessels and myocardial tissue in NRP myocardial injury.

4. Summary and prospect

The pathogenesis of traditional Chinese medicine involved in NRP are vein damage, blood stasis blocking heart pulse and heat toxin injury, which are causal and interactive, and are associated with the complex network signal pathway composed of many factors. It has been proved by modern scientific and technological examination that monomer, compound prescription and external treatment of traditional Chinese medicine play a better role in all stages and pathological types of NRP. According to individual differences, dialectical treatment is mainly based on removing blood stasis and dredging pulse, clearing heat and detoxification. Compared with simple western medicine treatment,the curative effect of combination of Chinese and western medicine is better.

But at present, there are still some deficiencies in the treatment of traditional Chinese medicine: ① the research report on the treatment of NRP with traditional Chinese medicine is insufficient, and the traditional Chinese medicine prescriptions and compound prescriptions in the study are combined with conventional western medicine. ② Although the isolated monomer components of traditional Chinese medicine have been proved to be effective,the effectiveness of traditional Chinese medicine prescriptions and the complex interaction between drugs are difficult to be analyzed by modern technology.

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