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REVIEW

Construction of the vessel-collateral theory and its guidance for prevention and treatment of vasculopathy

Yiling Wu[1,2]

[1] *Integration of Traditional and Western Medical Research Academy of Hebei, Shijiazhuang 050035, China;* [2] *Key Research Center of State Administration of Traditional Chinese Medicine (Cardiovascular Collateral Disease), Shijiazhuang 050035, China*

Abstract **According to the self-discipline of traditional Chinese medicine, vessel-collateral theory was constructed systematically, which was important to improving prevention and treatment level of vasculopathy. The hypothesis of "homeostasis (*Cheng*), compensatory auto-adaptation (*Zhi*), regulation (*Tiao*) and equilibrium (*Ping*)" based on the "qi–yin-yang–five elements" coupled with the *ying* (nutrients)-*wei* (defense) theory, has become the core content of the vessel-collateral theory. Clinical and laboratory trials have been developed to further confirm the scientific connotations of the hypothesis, such as *Tong Xin Luo* capsule, as the representative drugs of vessel collateral theory, showed good efficacy in protecting the vascular endothelium, stabilizing the vulnerable plaque and reducing the blood vessel spasm. "Sou, ti, shu, tong" was the characteristics of *Tong Xin Luo* capsule in treating "microvascular damage" as the core mechanism of acute myocardial infarction, cerebral infarction and microvascular complications of diabetes. *Shen Song Yang Xin* capsules in the treatment of arrhythmia have made integrated adjustment advantage. *Qi Li Qiang Xin* capsules have been made treating both manifestation and root cause of chronic heart failure. These research have improved prevention and treatment level of major vascular system diseases.**

Keywords vessel-collateral theory; vasculopathy; prevention and treatment

Introduction

According to the WHO statistics in 2000, approximately 17 million people in the world died of cardiovascular diseases each year. The *Statistical Gazette on Healthcare Development in China* issued by the Ministry of Health of China has indicated that the mortality and proportional mortality indicator of cardiovascular diseases have both ranked No. 1 since 1990, which took up 40% of the total death toll. Additionally, the *Annual Reports of Cardiovascular Diseases in 2006* has shown that every year 2 million people develop cerebral apoplexy, 500 000 people develop myocardial infarction and almost 3 million people die of cardiovascular diseases. In China, with distinctive features of "three highs and three lows" —high incidence, high disability rate, high mortality, low awareness, low control rate and low recovery rate, cardiovascular diseases have become the No. 1 killer endangering human life and health. As a result, they require cooperative and emergent measures from integrative Chinese and Western medicine.

The explanations of the complicated life and disease using reductionism thinking have been increasingly challenged by the emergence of global complexity science. Subsequently, it has become the core driving force of life science in the 21st century to return to holism and explain or interpret living organisms using nonlinear science, complexity system and systems biology. Deeply rooted in clinical practice, early philosophical thinking of "extending one's knowledge through investigation (*Ge Wu Zhi Zhi*)" and body dissection, traditional Chinese medicine contains ancient philosophical ideas of qi–yin-yang–five elements. It combines the metaphysical "qi" with anatomical "blood" and understands the internal law of life activities and disease development and progression from a holistic, systematic, dialectical and constantly changing perspective. In this regard, traditional Chinese medicine is of practical significance to shift from reductionism to holistic system study, therefore, creating an opportunity for innovative advance in prevention and treatment of cardiovascular diseases.

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Correspondence: yiling@yiling.cn

Systemic construction of the vessel-collateral theory

The vessel-collateral theory studies the occurrence and development law, essential pathology, clinical signs and symptoms, pattern identification, and treatment of "vessel collateral-vascular system conditions." The vessel-collateral conditions can result either from the functional or structural injury to the vessels and collaterals or from pathogenic factors as well as secondary pathology of the zang-fu organs or tissues, covering a wide range of cardio-cerebrovascular diseases, arrhythmias, chronic heart failure, pulmonary heart conditions, rheumatic heart disease and peripheral angiopathy. Common examples are cardiac pain due to chest-*bi* impediment, stroke, palpitations, cardiac fullness, edema due to heart yang deficiency, thoracic fluid retention, cardiac obstruction, and gangrene. Unfortunately, the conceptual confusion between "meridians and vessels" and "meridians and collaterals" originating from the historical prejudice on "collaterals" and "vessels" substantially compromised the importance of vessel-collateral theory and its resultant guidance for the prevention and treatment of vasculopathy. Consequently, constructing a systemic vessel-collateral theory helps to perfect the theoretical meridian system and further improve the prevention and treatment level for vasculopathy.

Actually, as pathways of circulating qi and blood, meridians are associated with the zang-fu organs and connect the upper body with lower body and the interior with exterior. The *Nei Jing* (Inner Classic) states that, "meridians are located in the deeper area, while collaterals are the transverse branches of the meridians and minute collaterals are subdivided branches of the collaterals." In other words, collaterals diverge from the meridians and contain different layers. They are extensively distributed over the zang-fu tissues, like a network system to maintain life activities and homeostasis of the organism.

Collaterals are further divided into meridian collaterals (qi) and vessel collaterals (blood). The former transports qi, while the latter transports blood. The two constitute two major interdependent but interactive networks to perform the physiologic functions of "circulating qi and blood as well as nourishing yin and yang." With combined vessel collateral and meridian collateral theory, the academic system of Chinese medicine consists of the *zang xiang* (core), meridians (pivot) and qi and blood (foundation). The concept of "blood vessel" was clearly mentioned in the *Nei Jing*. Other than a network for transporting blood, the "vessels" are the pathways of heart (lung)-blood-vessel circulation system and also an independent solid organ — an extraordinary fu-organ. Morphologically, vessels are empty cavities and associated with the heart and lung. Categorized into veins and arteries, vessels are reticulately distributed in multiple layers. Physiologically, vessels store and preserve essential qi to maintain a relative homeostasis of blood volume and quality. Kinetically, vessels dilate and contract following the heart beats. Functionally, vessels transport blood to nurture the whole body, help metabolism and promote interchange between fluid and blood. For the first time in history, the *Shang Han Za Bing Lun* (*Treatise on Cold Damage and Miscellaneous Diseases*) recorded the concept of "vessel collateral," discussed the vessel-collateral conditions, initiated the collateral-unblocking formulas and thus laid the theoretical, diagnostic and therapeutic foundation of vessel-collateral theory.

The vessel-collateral theory is distinctively characterized by the connotation of ancient philosophical ideas. The *Yi Jing · Xi Ci* (one chapter from the *Book of Changes*) records that, "whatever metaphysical are referred to as *Dao* — philosophical methods or thinking activities; whatever physical are referred to as *Qi* —objective, tangible things." The invisible qi, an ancient philosophical concept, is endued with a specific meaning in Chinese medicine: qi warms the body. The visible blood and vessels in anatomy nourish the body. As a result, the "qi-blood correlation" formed by philosophical idea, dissection confirmation and clinical practice has become a key part of the vessel-collateral theory. Of the subtypes of qi, *yuan*-primordial qi is known as the driving force of vital activities, while *zong*-pectoral qi runs through the heart vessel and is further divided into *ying*-nutrient qi and *wei*-defensive qi. The *ying*-nutrient qi flows within the vessel, whereas *wei*-defensive qi flows outside the vessel. The theory on *ying*-nutrients and *wei*-defense can be traced back to a couple of classics, for example, "disharmony between the *ying*-nutrients and *wei*-defense may result in blood stagnation" (recorded in the *Shang Han Lun*), "retention of pathogenic factors in vessels may cause blood stagnation" (recorded in the *Jin Kui Yao Luo*/*Essentials from the Golden Cabinet*) and "heart conditions can be treated by harmonizing the ying-nutrients and wei-defense" (recorded in the *Nan Jing*/ *The Classic of Difficult Issues*).

Normal vital activities including substance metabolism and energy transformation depend on the ascending, descending, exiting and entering of qi as well as the resultant qi transformation. This follows the law of dynamic yin-yang equilibrium and inter-promotion and inter-restraint among the five elements. The hypothesis of "homeostasis (*Cheng*), compensatory auto-adaptation (*Zhi*), regulation (*Tiao*) and equilibrium (*Ping*)" based on the "qi–yin-yang–five elements" summarizes the process of vital activities in terms of auto-adaptation, auto-regulation, homeostasis, compensatory auto-adjustment, disease treatment and therapeutic effect. The aforementioned four words *Cheng, Zhi, Tiao and Ping* expound how Chinese medicine understands life, disease, treatment and prognosis in varying levels. This, coupled with the *ying* (nutrients)-*wei* (defense) theory, has become the core content of the vessel-collateral theory, which can be explained that the ultimate goal of equilibrium can be restored by homeostasis between *ying* (nutrients)-*wei* (defense), compensatory auto-adjustment or unblocking the collaterals. This can

also shed new light on understanding human body as a complicated macrosystem and vasculopathy as complicated conditions regarding the physiology, pathology, treatment and prognosis.

The causative factors, pathogenesis, pattern identification and treatment of "vessel-vascular system conditions" have been analyzed using the above hypothesis. It asserts that major pathogenic factors include abnormal weather changes (contraction of six external pathogens), social psychological stress (seven emotional injuries), environmental pollution (toxins damaging the vessels), irregular lifestyle (work-rest imbalance) and build-up of metabolic products (phlegm-turbidity with stagnant toxins). In addition, it summarizes eight essential pathomechanism for collateral conditions, including collateral-qi stagnation (or deficient stagnation), stasis obstruction of the collaterals, contracture of the collaterals, stasis blockage of the collaterals, collateral masses, toxic-heat retention, impairment of the collaterals and deficiency and malnourishment of the collaterals. Since "blockage or obstruction" is considered as the pathogenic nature of "vessel-vascular system conditions," the general treatment principle is to "unblock the collaterals" by harmonizing *ying*-nutrients and *wei*-defense, regulating qi, blood, yin and yang and regulating qi of the five-zang organs as well as qi activities. Accordingly, common medicinals for the vessel-vascular system diseases are categorized by their functions. Simultaneously, eight major patterns and treatment based on identification of the zang-fu organs are also established. In summary, the pattern identification and treatment system within the frame of vessel-collateral theory is of significant guidance for vessel-vascular system diseases that greatly endanger human life and health.

Guidance of the vessel-collateral theory for prevention and treatment of vasculopathy

By combining the philosophical ideas of "qi–yin-yang–five elements" and "qi-blood correlation" with leading edge research advance, clinical and laboratory trials have been developed to further confirm the scientific connotations of the hypothesis of "homeostasis (*Cheng*), compensatory auto-adaptation (*Zhi*), regulation (*Tiao*) and equilibrium (*Ping*)." Clinical investigation of 3469 vasculopathy cases has been conducted using entropy-based complex system analysis and unsupervised data processing on clinical symptoms to avoid subjective bias from literature or expertise. In addition, the qualitative and quantitative criteria for pattern identification have been set up concerning pathologic links, such as, disease location, disease nature, patient, and disease tendency. The results on common pathogenesis and disease progression for vessel-vascular system diseases are reported as follows: collateral-qi stagnation or deficient stagnation runs through the whole process as a primary contributing factor; and phlegm, stasis and heat are pathological products and secondary pathogenic factors. As a result, common pathological links [1,2] include stasis obstruction of the collaterals and atherosclerosis, contracture of the collaterals and angiospasm, and stasis blockage of the collaterals and blood vessel occlusion. Additionally, the hypothesis of "homeostasis (*Cheng*), compensatory auto-adaptation (*Zhi*), regulation (*Tiao*) and equilibrium (*Ping*)" is now employed to guide one of the Major State Basic Research Development Program of China (973 Program) —Basic Research on Construction of Vessel-Collateral Theory and Its Guidance for Prevention and Treatment of Vasculopathy. Further research, which is based on the correlation between *ying*-nutrients qi and vascular endothelial function, *wei*-defensive qi and general NEI network and extensive regulation of tunica externa nerves, has been developed on interaction between *ying*-*wei* crossing and tunica externa and between NEI network and tunica intima.

Collateral-qi stagnation/deficient stagnation and vascular endothelial dysfunction

Simulated clinical investigation on patterns of deficient stagnation of collateral qi (due to overexertion, physical inactivity and anoxia) and collateral-qi stagnation has shown that collateral qi stagnation/deficient stagnation (social psychological factor) is a major risk factor for vascular endothelial dysfunction. Nonlinear additive effect occurs when the above pattern combines with the endothelial dysfunction model induced by high homocysteric acid. As a major factor contributing to the general NEI network disorder, the collateral qi stagnation/deficient stagnation also aggravates the vasculopathy via the general NEI network homeostatic mechanism disturbance. This result is of great significance in studying the risks of social psychological factors, such as mental stress or fatigue due to faster pace of life and intense competition. In addition to repairing localized vasculopathy, compound collateral-unblocking medicine can also regulate the NEI network: compound *Tong Xin Luo* (Heart Collateral-Unblocking Capsule) can obtain a similar effect as Simvastatin in improving the pathological injury to localized vascular endothelium; however it can obtain a significantly better effect than Simvastatin in regulating the whole NEI network.

Stasis obstruction of the collaterals and atherosclerosis

Clinical observations on pathological process of atherosclerosis (As) have suggested that injury to tunica externa can initiate and aggravate As through affecting the tunica intima and tunica media; neuroendocrine, oxidative stress and inflammatory immune reaction play a key role; MAPK-NF-κB is probably the common signal transduction pathway; and collateral-unblocking intervention can work effectively for As [3,4] via regulating sympathetic/parasympathetic nerve imbalance and inhibiting oxidation, inflammation

and immunolesion. For stabilizing the vulnerable lesion, collateral-unblocking intervention can regulate lipid, decrease the contents of lipid, adjust collagen, counteract inflammation and oxidation and thus reduce risk factors causing vulnerable lesion. Results have shown that this intervention can decrease the lesion rupture rate of 73% in the model group to 7.1%, showing no statistical difference with Simvastatin (7%) and presenting a relative equilibrium with the coexistent pathological injury [5]. This study has been published in the *Am J Physiol Heart Circ Physiol*, along with a commentary saying that, this study also highlights certain exciting possibilities in the management of patients who are at risk of developing clinical manifestations of coronary heart disease [6].

Contracture of the collaterals and angiospasm

Intravenous dripping of ET-1 can induce angiospasm, which is associated with the coronary artery smooth muscle Rho kinase, protein kinase C-δ and increased expression of NF-κB mRNA. *Tong Xin Luo* can increase the levels of endothelium-derivative relax factor NO and TXA_2, decrease the levels of contraction factor endogenous ET-1 and PGI_2, elevate the overall anti-oxidation ability and reduce the MDA level. It can obtain a similar effect as Diltiazem and Fasudil in relieving the angiospasm. Animal models of angiospasm induced by wrapping up the tunica externa of carotid artery with silica gel tube have shown that angiospasm was triggered by intensified vasoconstriction resulting from AngII elevation, RASS activation, increase of oxidative damage and subsequent activation of Rho/RhoK signal pathway. *Tong Xin Luo* can decrease the angiospasm incidence of 91% in the model group to 17% [7,8] by inhibiting the generation of AngII, reducing the vessel wall AT1R expression, increasing AT2R protein expression, decreasing the vessel wall p22phox protein expression, inhibiting the synthesis and activity of RhoK and thus increasing the blood volume of carotid artery.

Stasis blockage of the collaterals and blood vessel occlusion

According to the vessel-collateral theory, "micro-vascular injury" is regarded as a common core factor for acute myocardial infarction, cerebral infarction and diabetic capillary complications. As a result, medicinals with the function of resolving blood stasis and unblocking collaterals presented distinctive advantages in protecting the capillary function and structural integrity. Action mechanism study on protection of no-reflow capillaries in acute myocardial infarction has proven that *Tong Xin Luo* can protect the structural and functional integrity of capillary endothelial cells, relieve capillary spasm, inhibit micro-thrombus, counteract inflammation and oxidation, protect myocardial and peripheral microenvironment following reperfusion of AMI via regulating multiple pathologic links, enhance the repairmen of the organism and localized myocardial lesion and thus prevent the occurrence of myocardial no reflow. For the treatment of cerebral infraction, a new strategy for capillary protection in ischemia area was put forward. *Tong Xin Luo* can protect the structural and functional integrity of capillaries in ischemic area, promote remedial regeneration of blood vessels, enhance the opening of collateral circulation and thus protect the brain tissue. This has provided solid evidence for the treatment of cerebral infarction through protecting the capillaries. The idea of protecting the vascular nerve units through protecting brain and the capillaries in ischemia area opened a new path for the treatment of cerebral infarction other than thrombolysis and neuroprotection. In addition, *Tong Xin Luo* can also obtain marked effect for diabetic nephropathy, diabetic perineuropathy and diabetic cardiomyopathy, indicating a good perspective in treating intractable conditions. Other than that, *Tong Xin Luo* also obtained accurate effect for dementia, which initiated a new pathway for dementia through protecting capillaries. Studies on three major vascular conditions and good effects by collateral-unblocking intervention have proven the guidance and application value of the vessel-collateral theory [9–13].

Arrhythmias and chronic heart failure

The formula of *Shen Song Yang Xin* Capsule (Ginseng and Nardostachys Root Capsule) was based on the hypothesis of "*ying-wei* homeostasis (*Cheng*), compensatory auto-adaptation (*Zhi*), regulation (*Tiao*) and equilibrium (*Ping*)" to the study of arrhythmias and Ye Tian-shi's experience of "reinforcing and unblocking" in selecting medicinals as well as the general treatment principle of "warming, clearing, reinforcing and unblocking." Multicenter, prospective and randomized double-blind evidence-based clinical trials on 1476 cases with arrhythmias were conducted in 36 top-class hospitals led by Beijing Fuwai Hospital, First Hospital Affiliated to Nanjing Medical University and Beijing Chaoyang Hospital, using 24 h Holter as the main evaluation index. The results have shown that *Shen Song Yang Xin* Capsule obtained a higher total effective rate for ventricular premature beats than Mexiletine and a similar total effective rate for paroxysmal atrial fibrillation as Propafenone; moreover, it showed better results in improving clinical symptoms. For bradyarrhythmias, *Shen Song Yang Xin* Capsule obtained a total effective rate of 63.5% and could increase the ventricular rate by 7.09 times/min. Unlike the adverse reaction rate of 5.1% in the control group, there was none in the observation group.

The formula of *Qi Li Qiang Xin* Capsule (Astragali and Pepperweed Seed Heart-Strengthening Capsule) was based on the treatment principle of "supplementing qi, circulating blood and resolving edema." Control study with first-line Western drugs including cardiotonic agents, diuretics, angiotensin converting enzyme inhibiter, β acceptor blocker and angiotensin receptor antagonists have shown that this

capsule can obtain a similar cardiotonic effect as digoxin but a significantly better effect than Ramipril in inhibiting RASS and reducing Ang II level. It can obtain a similar diuresis effect as oral fursemide but a significantly better effect than fursemide in decreasing kidney aquaporin-2. In addition, it is substantially superior to Metoprolol in inhibiting ventricular remodelling. This embodied the drug combination in Western medicine for chronic heart failure and indicated the characteristics of *Qi Li Qiang Xin* Capsule in working for both the root cause and clinical manifestations.

All above studies have proven the guidance, scientific value and future application potential of "*ying-wei* homeostasis (*Cheng*), compensatory auto-adaptation (*Zhi*), regulation (Tiao) and equilibrium (Ping)" hypothesis, which is the core of the vessel-collateral theory. In addition, this may also become a key idea for multidisciplinary study on vasculopathy, which can not only guide the occurrence theory and intervention strategy of vessel-collateral conditions but also guide the nature of the complex vascular system diseases.

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