Research Progress of Traditional Chinese Medicine on Cardiac Remodeling

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ABSTRACT

Cardiac remodeling, secondly react to myocardium injure, is considered as a functional, compensatory and adaptive response initially, but continuously, persistently pathological stimulation can lead to cardiac disease. In Asian countries, people treated with heart disease with Traditional Chinese Medicine, including formulas, compounds extracted from Chinese herbs and acupuncture for long time. In this chapter, we review clinic and pharmacological research in recently, most aspects of the cardiac remodeling, such as cardiac function, cardiac pathophysiology and relevant mechanisms are involved.

Keywords: Traditional Chinese Medicine, Compound, Formula, Acupuncture, Cardiac remodeling, Mechanisms

INTRODUCTION

In 1982, The term "remodeling", as a process of pathology, was described in a myocardial infarction model for the first time, with the characteristics of resorption of necrotic tissue, laying down of granulation tissue and scar formation. At that time, the authors considered that remodeling generally preserved normal left ventricular (LV) contour [1]. In 2000, cardiac remodeling was published by an international forum and defined as genome expression resulting in molecular, cellular and interstitial changes and manifested clinically as changes in size, shape and function of the heart resulting from cardiac load or injury. Cardiac remodeling is influenced by hemodynamic load, neurohormonal activation and other factors still under investigation [2]. The concept of remodeling itself is initially functional, compensatory and adaptive in nature but, when sustained progresses to structural changes become self-perpetuating and pathogenic. Remodeling involves not only responses of the specific cardiovascular cells: cardiomyocytes, endothelium, smooth muscle cells, but also the interstitial cells and matrix [3]. Preventing or reversing cardiac remodeling is a key strategy for the treatment of heart failure and further efforts are highly needed to explore the mechanisms underlying cardiac remodeling.

TCM, including herbal formulas and acupuncture, has a history of more than 2500 years with a unique theory of diagnosis and treatment in orient Asian countries. In recent years, a lot of clinical and pharmacological researches were reported in cardiac area, particularly in cardiac remodeling and heart failure. Among them, compounds, represented by ginsenoside Rb1, tanshinone IIA, higenamine, curcumin, oxymatrine and herbal formulas containing prescribed Chinese herbs with named ratio, represented by Qiliqiangxin, Qishenyiqi, Shenfu Injection, Wenxin granule were all obtained plenteous achievements in improving cardiac function and reversing cardiac remodeling through multiple signaling pathway. So far, acupuncture therapy considered as a characteristic of TCM also has made a significant contribution for preventing and treating HF especially in the system of neural reflex such as inhibiting cardiac sympathetic afferent reflex (CSAR) and renal sympathetic nerve activity (RSNA) in chronic heart failure (CHF) rats after electro acupuncture [4].

THE INFLUENCE OF TCM COMPOUND, FORMULA AND ELECTROACUPUNCTURE FOR PATHOPHYSIOLOGY OF CARDIAC REMODELING

Pathophysiological Mechanisms of Cardiac Remodeling

The clear mechanisms of cardiac remodeling inducing the alteration of pathophysiological are not fully understood, several research areas like myocytes death, energy metabolic abnormalities, oxidative stress, calcium transportation, inflammation, cardiac extra cellular matrix (ECM), neurohormonal activation attracted more attention in recent years.

Myocytes Death

The sustaining loss of myocytes is a core process which results in cardiac remodeling and cardiac dysfunction gradually, whatever type of death, apoptosis, autophagy or necrosis. Lots of compounds extracted from Chinese herbs can protect myocytes from death. As follows, Wu et al. [5] demonstrated that higenamine, a compound from radix aconite, inhibits cardiomyocyte apoptosis in vitro using both neonatal and adult cardiomyocytes as well as ex vivo and in vivo mouse I/R models. Through the study of mechanism they found that anti-apoptotic effect of higenamine is mediated by the β2-AR/PI3K/AKT cascade. Cheng et al. [6] confirmed that in heart failure mouse/rat, remote ischemic conditioning (RIC) therapy combined with Astragaloside IV, the major active component extracted from Huangqi (Radix Astragali Mongolici), treatment yielded the most optimal protective effects through protecting apoptosis after acute myocardial infarction. Meanwhile, these results indicated that the anti-apoptotic function of Astragaloside IV closely related to Bcl-2/Bax signaling pathway. Geng et al. [7] demonstrated that curcumin, a polyphenol extracted from turmeric, has protective effect of anti-apoptotic in mice model of MI and hypoxia-induced cardiac myocytes is through the up-regulation of miR-7a/b and the down-regulation of SP1 expression. Chen et al. [8] showed that in mice model of MI, the inhibition of myocardial apoptosis by Schisandrin B, the most abundant dibenzocy-clooctadiene derivative in schisandra chinensis, is associated with the increased Bcl-2/Bax ratio and down-regulated apoptosis signal-regulating kinase 1 (ASK1) similarity to the study in H9c2 cells after hypoxia stimulation. Zhao et al. [9] confirmed that baicalein, a compound of flavone extracted from scutellaria baicalensis Georgi's dry root, could inhibit the apoptosis by reversing the repression of mitochondrial membrane potential, down-regulating the expression of cleaved caspase-3 and up-regulating the ratio of Bcl-2/Bax.

In the study of herbal formula, the expression of Bax was significantly decreased while Bcl2 expression was significantly increased in Qiliqiangxin (QLQX)-treated MI mice, leading to an increased Bcl2/Bax ratio, which in turn inhibited myocardial apoptosis. QLQX formula is made up of 11 distinct herbs, including astragali radix, ginseng radix et rhizoma, aconiti lateralis radix preparata, salvia miltiorrhiza radix et rhizoma, semen descurainiaelepidii, alismatisrhizoma, polygonatiodoratirhizoma, cinnamomi ramulus, carthami flos, periploca cortex, and citri reticulatae pericarpium [10]. Another research of herbal formula observed that a large number of myocardial apoptotic nuclei in the MI model while this phenomenon is significantly reduced in the presence of Wenxin Granule. Wenxin Granule contains Radix Codonopsis Pilosulae, Rhizoma Polygonati, Radix Notoginseng, Succinum and Radix et Rhizoma Nardostachyos [11].

Recently, an experiment on electroacupuncture (EA) showed that moderate stimulation at LR3 (Taichong), located between the first and second metatarsal bones on the dorsum of the foot, significantly reduce the cellular apoptosis in the LV tissue using the spontaneously hypertensive rat (SHR). Interesting, EA has an impact on some recognized markers of apoptosis, like decreasing

the death receptor FAS and its associated protein FADD; mitigating pro-apoptotic Bcl-2 family member Bax and the downstream protein cytochrome C; reducing Gαq and calcineurin which are proteins of the IGF2R dependent apoptotic pathway[12] (Table 1).

Table 1: Traditional Chinese medicine and its mechanism related to myocytes death.

Major phenotype	Compound, Formula and EA	Relevant mechanism
Myocytes Death	Higenamine (radix aconit)	β2-AR/PI3K/AKT
	Astragaloside IV (Radix Astragali)	Bcl-2/Bax
	Curcumin (turmeric)	miR-7a/b and SPI
	Schisandrin B (schisandra chinensis)	Bcl-2/Bax and ASKI
	Baocalein (scutellaria baicalensis Georgi's dry root)	Bcl-2/Bax
	Wenxin Granule	Ang II ?
	Qiliqiangxin	Bcl-2/Bax; Ang II ?
	EA at LR3 (Taichong)	FAS FADD; Bcl-2/Bax; Gαq and calcineurin

Energy Metabolic Abnormalities

Energy deficit is one of the vital factors which promotes further development of cardiac remodeling. Mitochondria is a core organelle in energy metabolism, when energy metabolic abnormalities ultimately result in mitochondrial atrophy and mitochondrial dysfunction [13]. Zheng et al. [14] reported that ginsenoside Rb1, a bioactive components of ginseng, signicantly inhibits HF-induced mitochondrial depolarization and apoptosis, suggesting that ginsenoside Rb1 attenuated HF-induced mitochondrial dysfunction by activating Akt pathway. A study by Li et al. showed that sesamin, the major lignan in sesame seeds, remarkably attenuates the lesions of mitochondria and eliminates mitochondrion vacuolizationin the left ventricular tissue of spontaneously hypertensive rats (SHRs) model [15].

Research on formula Qiliqiangxin (QLQX) demonstrated that mitochondria ultra structure of cardiac myocytes presents more swelling and vacuolization in SHRs, which could be greatly improved by QLQX treatment. QLQX might probably improve cardiac energy metabolism in SHRs via increasing PPARs and PGC-1α [10]. In TAC model, failing hearts present mitochondrial morphological alteration and disorganized cristae, and disorganized Z-line structures, but this kind of mitochondrial morphology and Z-line structures are nearly normal after treatment with Tongxinluo (TXL). TXL seems to improve the function of mitochondria indirectly by protecting the structure of mitochondria. TXL is derived from a group of herbal medicine including ginseng, radix paeoniaerubra, borneol, and spiny jujuba seed [16] (Table 2).

Table 2: Traditional Chinese medicine and its mechanism related to energy metabolic abnormalities.

Major phenotype	Compound, Formula and EA	Relevant mechanism
Energy Metabolic Abnomalities	Ginsenoside Rbl (ginseng)	AKT
	Sesamin (lignan in sesame seeds)	-
	Qiliqiangxin	PPARs and PGC-1α
	Schisandrin B (schisandra chinensis)	Bcl-2/Bax and ASK1
	Tongxinluo	-

Oxidative Stress

Oxidative stress plays a fatal pathophysiological role in cardiac remodeling. In physiological conditions, there is a balance between reactive oxygen species production and antioxidant defense. In pathological conditions, immoderate reactive oxygen species are accumulated that cannot be eliminated by antioxidant systems [17]. A study have shown that baicalein, derived from the root of Scutellaria baicalensis Georgi, can reduce Ang II-induced oxidative stress in the heart. Moreover, they found that this effect is accompanied by inhibition of NF-κB/p65 signaling pathway [18]. Dong et al. [19] showed that polydatin, a resveratrol glucoside, can attenuated cardiomyocyte hypertrophy triggered by phenylephrine. Furthermore, this anti-hypertrophic effect of polydatin contributes largely to suppression of reactive oxygen species-ROCK signaling cascade. In the MI model, Gao et al. [20] proved that treatment with polydatin significantly increased GSH-Px activity and enhanced the activity of CAT, which suggests that polydatin may attenuate ventricular remodeling after myocardial infarction in coronary artery ligation rats through inhibiting peroxidation. According to a study, aldose reductase (AR) as a redox-sensitive cytoplasmic protein which is associated with oxidative stress could inhibited by lignan extracts in spontaneously hypertensive rats model [21].

In the study of herbal formula, Li et al. [22] demonstrated that a significant increase on MDA level and decrease on superoxide dismutase (SOD) activities were detected after coronary artery ligation, while Qi-shen-yi-qi (QSYQ) could significantly increase the levels of SOD and decrease the levels of MDA.QSYQ formula prepared from a composition of six herbs of TCM, including two star herbs: Radix Astragalimongolici ('huang-qi' in Chinese) and Salvia miltiorrhizabunge ('dan-shen' in Chinese), and four other adjunctive herbs: FlosLonicerae, Scrophularia, Radix Aconiti Lateralis Preparata, and Radix Glycyrrhizae. Wang et al. [16] reported that 8-OHdG, a cellular oxidative stress biomarker, as well as MDA are reduced by treatment with Tongxinluo (TXL) in pressure overload-induced heart failure model. Furthermore, TXL could upregulate HO-1 expression and decrease Nox4 an NADPH oxidase. Taken together, these data suggest that TXL affects the improvement of oxidative stress injury in pressure overload-induced heart failure involving activation of the VEGF/Akt/eNOS signaling pathway (Table 3).

Table 3: Traditional Chinese medicine and its mechanism related to oxidative stress.

Major phenotype	Compound, Formula and EA	Relevant mechanism
Oxidative Stress	Baocalein (scutellaria baicalensis Georgi)	NF-κB/p65
	Polydatin (resveratrol glucoside)	ROS/ROCK GSH-Px and CAT
	Sesamin (lignan in sesame seeds)	T-AOC, MDA, nitroturosine
	Lignan extracts	aldose reductase (AR)
	Qi-shen-yi-qi	SOD and MDA
	Tongxinluo	VEGF/Akt/eNO

Calcium Transportation

Abnormal calcium transports, such as decreased L-type calcium channels, ryanodine receptors, decreased calsequestrin and calmodulin kinase activity are also involved in cardiac remodeling [23]. The experimental results of Zhao demonstrated that baicalein could effectively inhibits the decreased expression and activity of SERCA, increased expression of p-CaMKII and NCX1, and the decreased expression level of RYR2 in HF. These results demonstrated that Ca2+ handling proteins were involved in the beneficial effect of baicalein against HF [9]. Zhang et al. [24] reported that stachydrine (STA), a major constituent of Leonurusheterophyllus sweet, markedly improve Ca2+ handling by reduce Ca2+-transient amplitude and prolong Ca2+-transient decay constant on neonatal rat cardiomyocytes exposed to norepinephrine, the mechanisms is related to inhibition of β-adrenergic receptor. Mao's study revealed that protein kinase D1 protein (PKD1) that can reduce the Ca2+ sensitivity of muscle filaments by the phosphorylation of troponin I is significantly decreased by treatment with Astragalus and Salvia extract [25].

About a single herbal formula research showed that in H9c2 cells and neonatal rat cardiomyocytes, Ang II plus Leu27-IGFII result in elevation in cytosolic calcium concentration and this elevation of intracellular calcium is downregulated by Codonopsis pilosula [26] (Table 4).

Table 4: Traditional Chinese medicine and its mechanism related to calcium transportation.

Major phenotype	Compound, Formula and EA	Relevant mechanism
Calcium Transportation	Baocalein (scutellaria baicalensis Georgi)	SERCA and p-CaMKII NCXI and RYR2
	Stachydrine (Leonurus heterophyllus sweet)	β-AR
	Astragalus and Salvia extract	PKDI
	Codonopsis pilosula	IGFII/IGFIIR

Inflammation

Anti-inflammation, as a potential target for therapeutic intervention, is always widely concerned. Various cardiac injury are often accompanied with inflammation, and then the relevant inflammatory mediators can induce the cellular growth, activation of metalloproteinases,

proliferation of fibroblasts, and progressive loss of myocytes by apoptosis [27]. Tan's results showed that puerarin, an isoflavonoid isolated from Kudzu roots, normalizes the ratio of phosphor-Ser312IκBα/IκBα as well as reduces plasma level of TNFα in hypertensive high salt rats, suggesting that long-term treatment with puerarin result in a mild reduction in SBP. Additionally they found an amelioration of acetylcholine and insulin-induced vasorelaxation with the inhibition of NFκB inflammatory pathway [28]. A study showed that an increased expression of the inflammation marker COX-2 and TLR4 protein level in diabetic hearts are all reversed by anthocyanins from purple rice extract [29]. Cheng observed that the expression of two pro-inflammatory cytokines TLR4 and its downstream protein NF-κB are significantly higher in AMI model which are downregulated by Astragaloside IV treatment, which is the major active component extracted from Huangqi [6]. Wang et al. [18] demonstrated that the expression of pro-inflammatory cytokines including interleukin-6, interleukin-1β, and tumor necrosis factor-α were significantly inhibited by baicalein. The data suggests that baicalein can reduce Ang II-induced inflammation in the heart. Chen et al. [8] reported that the expression of inflammatory mediators TGF-β1 and TNF-α are increased after MI and then decreased by treatment with Schisandrin B, which demonstrated that Sch B had anti-inflammatory activity.

QSYQ effectively down-regulate TNF-α and IL-6.These results demonstrate a notable anti-inflammation efficacy of QSYQ which is co-related with TNF-α/NF-kB signaling pathway [22]. Wang's study showed that the gene expression of iNOS and MPO increased in MI model can be significantly inhibited by Danshen Injection (DSI) suggesting the effect of anti-inflammatory. DSI is a traditional Chinese medicine extracted from the dried root and rhizome of Salvia miltiorrhiza Bunge [30] (Table 5).

Table 5: Traditional Chinese medicine and its mechanism related to inflammation.

Major phenotype	Compound, Formula and EA	Relevant mechanism
Inflammation	Puerarin (Kudzu roots)	TNFα; NFκB
	Anthocyanins (purple rice extract)	COX-2 and TLR4 protein
	Astragaloside IV (Huangqi)	TLR4/NF-κB
	Baicalein (scutellaria baicalensis Georgi's dry root)	IL-6, IL-1β, and TNF-α
	Schisandrin B (schisandra chinensis)	TGF-βI and TNF-α
	QSYQ	NF-α/NF-kB and IL-6
	Danshen Injection	iNOS and MPO

Cardiac Extracellular Matrix (ECM)

The dynamic equilibrium of cardiac extracellular matrix (ECM) is critical in the pathogenesis of cardiac remodeling. On one hand, myofibroblasts promote excess deposition of ECM components such as collagen and fibronectin leading to the deleterious cardiac remodeling. On the other hand, in the border of remodeling region, myofibroblasts also active matrix metalloproteinase (MMPs),

degrading peripheral ECM. Thus, Adjusting the balance of ECM degradation and accumulation become the key strategy to ameliorate cardiac remodeling [31]. Mao et al. [32] showed that the increased expression of MMP9 in cardiac fibroblasts that incubated with Ang II is inhibited by tanshinone IIA, a potent pharmacological compound extracted from Salvia miltiorrhizabunge, in a dose-dependent manner. In Wang's study, Hydroxysafflor yellow A (HSYA, the main chemical component of the safflower yellow pigments) significantly inhibits the development of cardiac remodeling after pressure overload by attenuating the expression of MMPs [33].

Tsai's research demonstrated that alpinate oxyphyllae fructus (AOF, an important traditional Chinese medicinal herb) pretreatment significantly suppresses the cardiac remodeling proteins, metalloproteinases (MMP9 and MMP2) and tissue plasminogen activator (TPA), which are induced by Ang II in H9c2 cells [34]. In diabetic mice, the expression of MMP-2 and MMP-9 are significantly downregulated, and TIMP-2 is upregulated leading to a lower MMP-2/TIMP-2 ratio. These changes of protein levels are markedly reversed by Shengmai San (SMS) treatment. Moreover, SMS can remarkably abrogate the accumulation of collagen. SMS exerts a protective effect against type 2 diabetes-induced myocardial fibrosis through the regulation of TGF-β1/Smads axis. SMS consists of Radix Ginseng (Panax ginseng, Araliaceae), Radix Ophiopogonis (Ophiopogon japonicas, Liliaceae), and Fructus Schisandrae (Schisandrachinensis, Schisandraceae) [35]. Chen and coworkers showed that TGF-β1, MMP-2 and MMP-9 are up-regulated after coronary ligature, but they are all significantly suppressed by the administration of Danhong injection (DHI) as well as collagen accumulation. These results suggest that DHI may attenuate myocardial fibrosis by maintaining the balance of ECM. DHI is a standardized product extracted from Radix et Rhizoma Salviae Miltiorrhizae and FlosCarthami [36] (Table 6).

Table 6: Traditional Chinese medicine and its mechanism related to cardiac extracellular matrix.

Major phenotype	Compound, Formula and EA	Relevant mechanism
Cardiac Extracellular Matrix (ECM)	Tanshinone IIA (Salvia miltiorrhizabunge)	ERK and IκB
	Hydroxysafflor yellow A (HSYA, safflower yellow pigments)	COX-2 and TLR4 protein
	alpinate oxyphyllae fructus (AOF)	IGF II/IIR
	Shengamai San	TGF-β1/Smads
	Danhong injection	TGF-β1 and TNF-α

Neurohormonal Activation

Sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) are acknowledged as the main systems involved in cardiac remodeling. Once the two systems is activated excessively, will result in adverse consequences such as cardiomyocyte hypertrophy and activation of fibroblasts, activation of growth factors and metalloproteinases, hemodynamic overload by vasoconstriction and water retention, increase in oxidative stress and direct cytotoxic

effect [27]. Huang et al. [37] reported their results that serum NE is higher in spontaneous hypertension rat while oxymatrine, extracted from the root of Sophoraeflavescentis (Kushen), arrest sympathetic nerves to release NE, indicating that the function of oxymatrine in antagonizing myocardial hypertrophy and fibrosis correlates with its decreasing sympathetic hyperactivity. Zheng et al. [14] reported that ginsenoside Rb1 significantly inhibited Ang II, ACE and AT1 receptor in a rat model of heart failure suggesting that ginsenoside Rb1protects rats against myocardial fibrosis. Mao's study showed that pre-treatment with tanshinone IIA inhibits expression of the AT1 receptor in Ang II-stimulated cardiac fibroblasts [32]. After MI, angiotensin I (Ang I) and angiotensin II (Ang II) concentrations of ventricular tissue and aldosterone (ALD) concentration in the serum are increased while these adverse effects significantly reversed by polydatin which is indicated that effection of polydatin is related to anti-neuroendocrine activation [20].

Wu et al. [11] reported that in MI model the serum Ang II concentration is significantly increased however Wenxin Granule could decrease the concentration of Ang II.Another research showed that Qiliqiangxin (QLQX) could reduce the production of angiotensin II and downregulate the expression of AT1-R in myocardium during pressure overload [38].

Huo et al. [39] showed that long term electroacupunctureat Baihui (DU20) and Zusanli (ST36), traditionally alone or in combination for treatment of hypertension, affect the rennin-angiotensin system by decreasing content of Ang II and ET-1 in the plasma and decreasing expression of ATIR and ETAR in aorta and myocardium in SHR (Table 7).

Table 7: Traditional Chinese medicine and its mechanism related toneurohormonal activation.

Major phenotype	Compound, Formula and EA	Relevant mechanism
Neurohormonal Activation	Oxymatrine (Sophorae flavescentis)	Ang II, ACE
	Ginsenoside Rb1 (ginseng)	Ang II, ACE and ATIR
	Tanshinone IIA (Salvia miltiorrhizabunge)	ATI
	Polydatin (resveratrol glucoside)	Ang I, Ang II, ALD
	Wenxin Granule	Ang II
	Qiliqizngxin	AngII and ATIR
	EA at Baihui (DU20) and Zusanli(ST36)	Ang II and ET-I ATIR and ETAR

CLINICAL APPLICATION

For thousands of years, Chinese medicine has been used to treat heart failure, which is widely recognized, because of relieving the symptoms of heart failure and improving the quality of life. Nowadays, Chinese medicine also can promote the curative effect and reduce side effects of western medicine.

In recent years, several clinical trials have shown that Shensong Yangxin capsules (SSYX), Qishen granules (QSG), tanshinone IIA sulfonate are all have the effect to improve cardiac function

[40-42]. A randomized clinical trial showed that there is no significant difference between QSYQ and aspirin in the secondary prevention of myocardial infarction, but QSYQ present lower side effects, such as hemorrhage and gastric acid reflux [43]. Another study also found that in addition to increasing the ejection fraction, LV end-diastolic volume index (LVEDVi) and LV end-systolic volume index (LVESVi) are significantly reduced treatment with Danlou tablets. Furthermore, the reduction of LVESVi is independent of beta-blocker, ACE inhibitors/ARBs use. What is worth paying attention to is that Danlou tablets reduces the incidence of the major adverse cardiovascular events [44]. Based on the sufficient evidence of fundamental research, more and more Chinese medicine will be developed and applied for the clinic.

CONCLUSION

In modern society, despite the therapy of western medicine advances, mortality rates related to cardiac remodeling remain high [45]. It is well known that multi-target interference approaches have been widely used in TCM for thousands of years and their efficiencies have also been proved. For example, in the same condition of reversing cardiac remodeling, lignan extracts displays an effect of long-term lowering SBP and QSYQ can down-regulate the pNFKB1 in dose-dependent manner, however the efficacy was not notable as captopril [21, 22]. Hence, there has been a growing interest in studying Chinese herbal medicine in many countries. The above results prove that TCM in cardiovascular disease prevention and treatment is a valuable and promising prospect. To research each compounds of Chinese medicine is a huge job, but it is beneficial to dissect the interactions within various compounds. Meanwhile, it is a pivotal approach to develop a new type medicine that could make a contribution to human health.

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