
Review Article

Chinese herbal medicine and acupuncture for the treatment of cardiovascular disease

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Traditional Chinese medicine (TCM) is one of the world's oldest healing systems. TCM includes herbal medicine, acupuncture, moxibustion, massage, food therapy, and physical exercise, such as shadow boxing. In modern China, TCM is a fully institutionalised part of health care and widely used with Western medicine. In 2006, the TCM sector provided care for over 200 million outpatients and some 7 million inpatients, accounting for 10-20% of health care in China.¹ Numerous studies conducted in China and some in other countries have shown that TCM significantly helps patients with coronary heart disease, hyperlipidemia, hypertension, pericarditis, angina pectoris, tachycardia, atherosclerosis, heart failure, and other circulatory conditions. Many doctors trained with Western medicine now recognize that a combination of Western therapy and TCM has shown better results in improving overall health in patients with cardiovascular disease (CVD) than have modern medicine drugs or surgery alone.² In this review, we present a brief outline of TCM for the treatment of CVD, focusing on the two most used TCM therapeutic modalities, Chinese herbal medicine (CHM) and acupuncture. There are huge amounts of Chinese publications on the use of CHM and acupuncture for CVD, but only those published in English will be reviewed here.

Traditional Chinese medicine

TCM is both an art and a systemic theory of patient-centered healing with combined attention to body, mind, and spirit. Knowledge of TCM has been enriched for over 4,000 years of observation and clinical experience. The philosophy of TCM is rooted in Chinese cultures of Taoism (to follow nature's way) and Confucius (to nurture humanity and morality) and the religion of Buddhism (to free from suffering). Traditionally, TCM doctors are usually pharmacists and pharmacologists who themselves identify and collect herbs, prepare formulation and follow up their

patients.³

In literature, TCM is characterized by individualized treatments based on the differentiation of syndrome (Zheng). CHM is the major modality in TCM practice. A prescription for CHM usually refers to a compound recipe (Fu Fang) that consists of principal, assistant, adjuvant, and guiding herbs to maximize therapeutic effects and minimize toxic effects. Ingredients in a CHM prescription are individualized and changed on a weekly basis to tailor for the patient's age, gender, symptoms, anthropological characters, geological location and living environment.⁴ The compounds extracted from Chinese herbal medicines include flavonoids, xanthenes, triterpenoids, alkaloids, glycosides, alkyldisulfides, aminobutyric acid derivatives, guanidine, polysaccharides, peptides, and minerals.⁵ In TCM, treatment effects are described differently, e.g., improved qi and blood flow; decrease in blood stasis and qi stagnation; decreased stagnation of cold in the chest; decreased phlegm, fluid, and damp accumulation; supplemented and nourished heart yin; strengthened heart qi; draining of heart fire; harmonized heart connections to other organs (not just anatomically speaking) such as kidneys, lung, pericardium, spleen, gallbladder, and small intestine; and reinforced and invigorated heart yang.

Acupuncture involves the insertion of needles and stimulation of acupoints that are located at lines of meridians that correspond to the flow of energy through the body. Modern acupuncture has evolved other methods of stimulating acupoints including the use of an electrical current, by applying pressure to the acupoint (acupressure) or using a low intensity laser. Texts on acupuncture date back to 206 BC, although the Yellow Emperor, Huang Di, the originator of TCM lived in 2,697 BC. During the past decades, acupuncture has gained increasing acceptance by the lay public, partly as a result of increasing communication between the U.S. and China since the early 1970s.^{4, 6} The mechanism by which acupuncture is believed to benefit the subject is through its ability to modulate neural activity in several regions of the brain and thus reduces sympathetic outflow to the heart and vascular system.⁷

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Chinese herbal medicine for the treatment of specific CVD

Heart failure

Although CHM has been widely used for the treatment of heart failure and thousands of studies have been reported, only a few were published in English, most of them were on a compound recipe: Sheng-mai-san (SMS), which is comprised of Radix Ginseng, Radix Ophiopogonis, and Fructus Schisandrae Chinensis. SMS has been clinically used for more than 800 years in China. According to Chinese medical theory, SMS is prescribed for replenishing vital energy, restoring the circulation, and sustaining body fluids. SMS is commonly used in patients suffering from coronary heart disease, cardiogenic shock, and congestive heart failure. A recent review of 19 clinical trials found that, compared to usual treatment alone, SMS injection plus usual treatment showed significant improvement in New York Heart Association classification of clinical status (RR 0.32; 95% CI 0.25 to 0.40), mortality (RR 0.25; 95% CI 0.07 to 0.86), hemodynamic tests, and tumor necrosis factor- α (WMD -0.52; 95% CI -0.99 to -0.05). No adverse effects were reported in any of the included trials. The authors concluded that it is possible that Shengmai plus usual treatment may be beneficial compared to usual treatment alone for heart failure, although the evidence is weak because of the poor quality of the included trials.⁸

Hypertension

TCM is widely used in the treatment of hypertension in China, whether in fixed or individualized recipe. Among CHMs, *Stephania tetrandra*, *Ligusticum wallichii*, *Uncaria rhynchophylla*, and *Evodia rutaecarpa* are more commonly used as hypotensive medicine. Tetrandrine, an alkaloid extract of *S. tetrandra*, has been shown to be a calcium ion channel antagonist, paralleling the effects of verapamil. Tetrandrine blocks T and L calcium channels, interferes with the binding of diltiazem and methoxyverapamil at calcium-channel binding sites, and suppresses aldosterone production. A parenteral dose (15 mg/kg) of tetrandrine in conscious rats decreases mean, systolic, and diastolic blood pressures for more than 30 minutes; however, an intravenous 40 mg/kg dose killed the rats by myocardial depression. In stroke-prone hypertensive rats, an oral dose of 25 or 50 mg/kg produced a gradual and sustained hypotensive effect after 48 hours without affecting plasma renin activity.⁷ In addition to its cardiovascular actions, tetrandrine has reported antineoplastic, immunosuppressive, and mutagenic effects.⁹

More recently, tetrandrine has been implicated in an outbreak of rapidly progressive renal failure, termed Chinese herb nephropathy. Numerous individuals developed the condition after using a combination of several Chinese herbs as part of a dieting regimen. It has been hypothesized that the cause may be attributed to misidentification of *S.*

tetrandra; nonetheless, questions still remain as to the role of *S. tetrandra* in the development of this serious toxic effect.¹⁰

The root of *L. wallichii* is used in TCM as a circulatory stimulant, hypotensive drug, and sedative. Tetramethylpyrazine, the active constituent extracted from *L. wallichii*, inhibits platelet aggregation in vitro and lowers blood pressure by vasodilation in dogs. With its actions independent of the endothelium, tetramethylpyrazine's vasodilatory effect is mediated by calcium channel antagonism and nonselective antagonism of α -adrenergic receptors. Some evidence suggests that tetramethylpyrazine acts on the pulmonary vasculature. Currently, there is insufficient information to evaluate the safety and efficacy of this herbal medicinal.¹¹

U. rhynchophylla is sometimes used in TCM to treat hypertension. Its indole alkaloids, rhynchophylline and hirsutine, are thought to be the active principles of *U. rhynchophylla*'s vasodilatory effect. The mechanism of *U. rhynchophylla*'s actions is unclear. Some studies point to an alteration in calcium ion flux in response to activation, whereas others point to hirsutine's inhibition of nicotine-induced dopamine release. One in vitro study has shown *U. rhynchophylla* extract relaxes norepinephrine-precontracted rat aorta through endothelium-dependent and -independent mechanisms. For the endothelium-dependent component, *U. rhynchophylla* extract appears to stimulate endothelium-derived relaxing factor and/or nitric oxide release without involving muscarinic receptors. Also, in vitro and in vivo studies have shown that rhynchophylline can inhibit platelet aggregation and reduce platelet thromboses induced with collagen or adenosine diphosphate plus epinephrine. Safety and efficacy cannot be evaluated at this time because of a lack of clinical data.¹²

E. rutaecarpa (wu-chu-yu) is a Chinese herbal drug that has been used as a treatment for hypertension. It contains an active vasorelaxant component called rutaecarpine that can cause endothelium-dependent vasodilation in experimental models.⁹

Coronary heart disease

In TCM, most cases of angina are considered to be caused by Xueyu (blood stasis) and/or Tanzuo (phlegm stagnation). Dozens of recipes have been used for the treatment of angina during the past decades. Among them, suxiao jixin wan, which composed of *Ligusticum chuanxiong* Hort. (chuanxiong) and *Borneolum syntheticum* (bingpian), and more recently, *Salvia droplet pill* (fufang danshen diwan) are most widely prescribed fixed compounds. A systemic review of 15 trials involving 1,776 patients showed that suxiao jixin wan improved ECG measurements (RR 1.16, 95% CI 1.05 to 1.27), reduced symptoms (RR 1.09, 95% CI 1.04 to 1.13), reduced the frequency of acute attacks of angina (difference in means -0.70, 95% CI -0.90 to -0.50), reduced diastolic pressure (difference in means -3mmHg, 95%

CI -5.73 to -0.27) and reduced the need for supplementary nitroglycerin in patients with angina pectoris.¹³

Salvia miltiorrhiza (dan-shen), a relative of the Western sage *Salvia officinalis*, is perhaps the most marketed CHM in China. The effects of dan-shen for the treatment of AMI and other CVD have been extensively reviewed recently.¹³ In TCM, the root of *S. miltiorrhiza* is used as a circulatory stimulant, sedative, and cooling drug. *S. miltiorrhiza* may be useful as an antianginal drug because it has been shown to dilate coronary arteries in all concentrations, similar to *Panax notoginseng*. Also, *S. miltiorrhiza* has variable action on other vessels depending on its concentration, so it may not be as helpful in treating hypertension. In vitro, *S. miltiorrhiza*, in a dose-dependent fashion, inhibits platelet aggregation and serotonin release induced by either adenosine diphosphate or epinephrine, which is thought to be mediated by an increase in platelet cyclic adenosine monophosphate caused by *S. miltiorrhiza*'s inhibition of cyclic adenosine monophosphate phosphodiesterase. *S. miltiorrhiza* appears to have a protective action on ischemic myocardium, enhancing the recovery of contractile force on reoxygenation. More recently, *S. miltiorrhiza* has been shown to protect myocardial mitochondrial membranes from ischemia-reperfusion injury and lipid peroxidation because of its free radical-scavenging effects. Qualitatively and quantitatively, a decoction of *S. miltiorrhiza* was as efficacious as the more expensive isolated tanshinones.^{14, 15}

The root of *P. notoginseng* is also often used in the treatment of patients with angina and coronary artery disease. Because of its resemblance to *P. ginseng* (Asian ginseng), *P. notoginseng* has acquired the common name of pseudoginseng, especially since it is often an adulterant of *P. ginseng* preparations. *P. notoginseng* has been described as a calcium ion channel antagonist in vascular tissue. More specifically, its pharmacological action may be as a novel and selective calcium ion antagonist that does not interact with the L-type calcium ion channel but rather may interact with the receptor-operated calcium ion channel.¹⁶

Arrhythmia

Numerous Chinese herbal medicines are identified to have antiarrhythmic effects, such as xin bao, ci zhu wan, bu xin dan, and several others.¹⁷ However, few clinical trials have been conducted to study their effects and safety. In one observational study, the effects of xin bao were documented in 87 patients with sick sinus syndrome. Xin bao was administered orally 2 to 3 times per day for 2 months. Patients with major symptoms of sick sinus syndrome, which included dizziness, palpitations, and chest pressure, improved significantly after treatment.¹⁸ No serious adverse effects were noted.

Shensong Yangxin (SSYX) is one of the compound

recipes of traditional Chinese materia medica including 12 ingredients such as *P. ginseng*, dwarf lilyturf tuber, nardostachys root, etc. Clinical study showed that SSYX could reduce the number of ventricular extrasystoles in patients with or without structural heart disease. Animal model showed that SSYX significantly inhibited the arrhythmias induced by toxic chemical compounds or ischemia-reperfusion injury. One of the mechanisms underlying SSYX's antiarrhythmic effects may be related to its action of blocking multiple ion channels such as INa, ICaL, IK, Ito and IK1, which may change the action potential duration.¹⁹

Acupuncture for the treatment of CVD

The World Health Organization (WHO) has noted that acute infection and inflammation, dysfunction of autonomic nervous system, pain, and peripheral and central neurological diseases each represent conditions for which acupuncture may be indicated. There are four areas of CVD for which acupuncture eventually may be indicated. These include ischemic CVD, hypertension, heart failure, and arrhythmias.²⁰

Coronary heart disease

Experimental studies indicate that acupuncture reduces demand-induced myocardial ischemia in felines, catecholamine- or stress-induced hypertension, or genetically associated hypertension. These studies also demonstrate that acupuncture limits myocardial ischemia by reducing myocardial oxygen demand rather than by increasing coronary blood flow in a feline model.^{21, 22} Studies from several groups have examined the role of acupuncture in treatment of patients with stable angina. Ballegaard and colleagues^{23, 24} showed an acupuncture-related improvement in exercise capacity and rate-pressure product, particularly when acupuncture reduces sympathetic neural outflow. Separately, Richter et al.²⁵ observed that acupuncture exerted a beneficial effect in patients with severe stable angina who had been aggressively treated with medical therapy. Manual acupuncture reduced the number of anginal attacks per week, the severity of chest pain, electrocardiographic evidence of myocardial ischemia, and increased the workload required to provoke angina in patients with CAD and stable angina. The latter study used a tablet placebo control. These studies involved small numbers of patients, were unblinded, and did not use the most appropriate sham controls.

Hypertension

The rationale for using acupuncture to treat myocardial ischemia, hypertension, and arrhythmias stems from its ability to inhibit sympathetic outflow. Several small trials suggest that hypertension may be improved by acupuncture. The magnitude of the effect of acupuncture on blood pressure in patients with hypertension is small but significant; reductions of 5 to 10 mm Hg have been noted. These and

other small studies from outside the U.S. have led to funding of at least two ongoing clinical trials by the NCCAM to test the hypothesis that acupuncture can lower blood pressure in patients with hypertension. Although there are no well-controlled studies in humans, there is a suggestion that one to four courses of 10 days' treatment with acupuncture lowers blood pressure (5 to 25 mm Hg) in some (e.g., borderline and essential hypertension) but not in all types of hypertension.²⁶

Two high-quality randomized controlled trials (RCTs) of acupuncture for hypertension have been recently published, but with conflict results. In the Stop Hypertension With Acupuncture Research Program (SHARP) trial comparing individualized (and standard) Chinese acupuncture with a sham procedure, blood pressure declined in each group between randomization and the 10-week follow-up, but the differences in achieved blood pressure reduction between groups were not significant. Thus, the authors concluded that there was no evidence of benefit of acupuncture for blood pressure lowering.²⁷ However, Flachskampf et al²⁸ report a single-institution, single-blind randomized controlled trial of 160 adult patients with grade 1 or 2 hypertension on stable blood pressure-lowering therapy or no therapy. Over a 6-week period involving a total of 22 treatment sessions, blood pressure-specific acupuncture was administered to intervention group subjects and sham acupuncture to control group subjects by Chinese physicians trained and accredited in Chinese traditional medicine. The authors report that the change in 24-hour ambulatory systolic blood pressure between baseline and 6 weeks (primary outcome) was significantly greater (-6 mm Hg) in the intervention group compared with the control group (1 mm Hg), although blood pressure in both groups returned to pretreatment levels within 12 weeks of treatment cessation. The authors conclude that acupuncture may offer an alternative antihypertensive therapeutic option especially in patients who want to avoid drug therapy or are attracted to the spiritual foundations of such a therapy.

Heart failure

In the first study to examine acupuncture in heart failure, Chen and colleagues²⁹ studied patients with 1) hypertrophic cardiomyopathy (n=24), 2) congestive cardiomyopathy (n=16), and 3) normal healthy control subjects (n=12). Acupuncture was compared at 2 sites bilaterally: 1) Neiguan (P6) and 2) Shaofu (H8). Electroacupuncture (EA) for 2 minutes was followed by retention of the needles in place for 15 minutes. Echocardiography, apex cardiography, and systolic time interval were used to assess cardiac performance before and after acupuncture. In 2 patients, pulmonary capillary wedge pressure was recorded. In the hypertrophic cardiomyopathy group, acupuncture at Neiguan was associated with an overall worsened cardiac performance. Left ventricular outflow diameter was diminished, stroke volume

and cardiac output were diminished significantly, and the pulmonary capillary wedge pressure increased. In contrast, in the congestive cardiomyopathy group, acupuncture at Neiguan improved parameters of cardiac function, specifically contractility. Left ventricular outflow diameter, stroke volume and cardiac output, and pulmonary capillary wedge pressure decreased. The opposite acute effects were seen after stimulation at Shaofu. That is, left ventricular outflow tract diameter increased in hypertrophic cardiomyopathy but decreased in congestive cardiomyopathy; stroke volume and cardiac output increased in hypertrophic but decreased in congestive cardiomyopathy. Acupuncture had no significant effect in normal subjects. The investigators concluded that acupuncture at the Neiguan point had an overall acute sympathomimetic effect, which could be acutely beneficial in congestive cardiomyopathy, whereas Shaofu appeared to be sympatholytic with similar effects to beta-blockers in hypertrophic cardiomyopathy. In a small, controlled but unblinded study, the acute effect of electroacupuncture at Neiguan or at an adjacent, nonacupoint site on the heart rate, blood pressure, and echocardiographic findings in 8 patients experiencing congestive heart failure was studied. After Neiguan stimulation, but not control stimulation, left ventricular end diastolic volume and stroke volume increase significantly. Heart rate, blood pressure, and ejection fraction remained unchanged after each type of stimulation. The investigators concluded that acupuncture at Neiguan improved ventricular relaxation, but in contrast to Chen's study, contractility was not affected by acupuncture at Neiguan.³⁰ In a study of a large, heterogeneous group of cardiac patients (n=107) and control subjects (n=100) without cardiac disease, the effects of needling at the left Neiguan point on left ventricular function was examined.³¹ In normal subjects, heart rate decreased significantly after needling, but other parameters of cardiac function remained unchanged. In cardiac patients, heart rate decreased, contractility increased, but ventricular relaxation remained unchanged. The explanations for the inconsistent findings in these studies can be found in their limitations of size, inadequate or absent controls, and unblinded design. To date, there are no large randomized, controlled trials of acupuncture in heart failure in which investigators interpreting echocardiographic and/or hemodynamic data are blinded and satisfactory acupuncture controls are used. The effects of chronic acupuncture in patients experiencing heart failure have not been studied.

More recently, Middlekauff et al.³² reported the effect of acute acupuncture in patients experiencing chronic heart failure. Ten patients with advanced heart failure underwent acute mental stress testing before and after "real" acupuncture at Neiguan (P6), Hegu (Li4), and Taichong (Liv3). Acupuncture needles were inserted and manually stimulated to achieve the De Qi sensation of heaviness, fullness, or soreness, and then left in place for 15 minutes. Mental stress

was produced by having the patient perform mental arithmetic and answer aloud or by the color-word conflict test. In this test, names of colors were written in a different color ink than the printed word. Patients were instructed to rapidly name the color, not read the word. Sympathetic nerve activity (MSNA) directed to the muscle vasculature was directly recorded from the peroneal nerve using the technique of microneurography. Resting MSNA was not different before and after acupuncture. During mental stress, MSNA increased by approximately 25%. This increase in sympathetic activity was eliminated after real acupuncture, but sympathetic activity remained unchanged with nonacupoint or no-needle acupuncture, eliminating the possibility of a placebo or time effect.

Arrhythmia

Early studies have showed acupuncture could inhibit ventricular extrasystoles induced by stimulating the hypothalamus, paraventricular nucleus or following administration of BaCl₂.³³ More recently, the same group reported that the enhanced arrhythmia score induced by global ischemia and reperfusion (SGIR) could be significantly attenuated by EA pretreatment. They also found that EA pretreatment attenuated the SGIR-enhanced response of [Ca(2+)](i) to the activators of adenylate cyclase, protein kinase A, and the L-type Ca(2+) channel in the myocytes isolated from the hearts subjected to SGIR.³⁴

Few clinical studies on treatment of arrhythmia with acupuncture have been published in English language. In a recent review of eight studies, VanWormer et al.³⁵ found that 87% to 100% of participants with arrhythmia converted to normal sinus rhythm after acupuncture. Acupuncture seems to be effective in treating several cardiac arrhythmias, including supraventricular tachycardia, sinus bradycardia, and ventricular extrasystole. The authors concluded that because of the limited methodologic quality of the studies, it is necessary to do better-controlled clinical trials to evaluate the role of acupuncture in the treatment of arrhythmia.

Conclusion and future directions

With the growing burden of CVD around the world, new approach should be integrated into the prevention and treatment strategy of this epidemic and TCM may play an important role. However, despite decades of research, the fundamentals of TCM remain largely unchanged and its theories inexplicable to science, which has caused skepticism and criticism. Recently, some randomized trials have shown efficacy for TCM for the treatment of CVD. But the quality of TCM trials should be improved. For example, it is important to compare TCM with a placebo or an intervention of proven efficacy rather than interventions with unknown effects. Furthermore, patients' inclusion and exclusion criteria, and indications and contraindications of the

tested therapy, must be specified clearly in a language comprehensible to users who have never learnt TCM. Tested herbal products also need to be standardized to ensure manufacturing consistency. Standardization is similarly important for diagnosis and procedural treatments, such as acupuncture.

International collaborations and dialogues between practitioners of TCM or Western medicine are important to further improve the scientific quality and clinical significance of TCM trials. Because TCM has long been in use, research could move to an efficacy-driven approach, in which TCM therapies are tested in trials on human beings first and studies on mechanisms of action and active substances should start only when efficacy is firmly shown.

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