

Present Researching Approaches and Future Prospects for Treatment of Cardiac Diseases - Integrative Medicine

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ABSTRACT

The pathogenesis of cardiac diseases is very complex and involved in many gene transcription and protein expression. How to effectively treat the diseases has become the hotspot of modern medicine. Accumulating evidences over the past decades on integrative medicine have shown us hopeful future prospects. With the development of modern biomedicine, such as sketch mapping genomic sequence, functional genomics, proteomics and pharmacogenetics, more advanced techniques could be applied in elucidating the possibly complicated biological networks, or complex pathological and physiological mechanisms underlying cardiac diseases, by which integrative medicine will also bring out some new and more effective strategies in the treatment of cardiac diseases.

Key words: Future prospects, Cardiac diseases, Integrative medicine, Treatment

Abbreviations: WM, Western Medicine; CDs, cardiac diseases; BP, blood pressure; TCM, Traditional Chinese medicine; CHM, Chinese herbal medicine; CHF, cardiac heart failure; PCI, post-percutaneous coronary intervention; CHD, coronary heart disease; ACS, acute coronary syndrome.

1. INTRODUCTION

Advanced techniques and drugs of Western Medicine (WM) applied in clinical practice have brought new hope for the treatment of the cardiac diseases (CDs). Retrospect to the whole picture of medical service, however, one sees few definitive treatments for these diseases. Take hypertension as an example; although five types of drugs were used to control blood pressure (BP), the target level of BP for patients with hypertension is still in debate, and numerous studies showed a J-shaped curve relationship between BP and adverse events (i.e. the lower the diastolic pressure, the greater the risk of coronary heart disease and adverse outcomes). For coronary heart disease, the 'residual risk'^[1] or ischemia symptoms still exist after revascularization and there is always a hard time during drug treatment due to the increase of serious side effects. Actually, WM may just improve the clinical symptoms or slow down some pathological progress but basically does not have any curable methods on them^[2, 3].

Recently, people have recognized that CDs as a chronic developing process are different from infectious diseases, which are characterized as follows: (1) its pathological and physiological changes often followed cardiac metabolism disorder and ageing; (2) the cause of the diseases may be associated with the interactions among the social, mental, inherited and environmental factors; therefore, it was very difficult to identify which one was the primary or secondary pathological factor; (3) the pathological changes were

complex, involving the abnormalities of metabolism, the disorders of the immune and neuro-endocrine systems which always happened in a sequence of chain reactions; and (4) the outcomes from the treatment on some identified pathological targets were not pleasing. Accordingly, people were encouraged to look for new methods suggested by integrative medicine. In this paper, we will discuss how integrative medicine takes part in the treatment of cardiac diseases in order to forecast its future prospects in it.

2. DEFINITION

2.1 Traditional Chinese medicine

Traditional Chinese medicine^[4] (TCM) is the valuable heritage of the outstanding Chinese national traditional culture and has been used as a medical approach in China for more than 2000 years. TCM is the product of combining Chinese medical experience with Chinese culture, which focuses on holism and naturalism.

2.2 Integrative medicine

Integrative medicine, about 50 years in the history of China, was formed since TCM and WM cannot meet the medical service requirements if they are used separately and independently⁴. It intends to integrate TCM and natural therapies with modern scientific findings even if it is hard to integrate both theoretical systems.

2.3 Western medicine

WM, which originated from the Western countries, is the biomedicine and has been used as a medical approach in the world for more than 200 years. WM is the product of combining modern natural sciences including medical sciences, biology and logic, which focuses on analysis and innovation.

3. PRESENT RESEARCH APPROACHES

Up to date, three characterized research approaches were used by integrative medicine as follows: (1) taking advantages of the advanced and scientific techniques to explore TCM (such as finding active ingredients in Chinese herbal medicine (CHM) or clarify its underlying mechanism); (2) combining TCM therapeutic methods with WM approaches in medical practice to improve clinical efficacy; (3) making use of TCM theory to explain the pathological and physiological changes found in WM researches. It is of no exception in the treatment process of CDs.

3.1 Exploring TCM

Over the past decades, a lot of drugs widely accepted in clinical practice came out from the efficient ingredients of Chinese herbs. For example, the discovery of artemisinin (qinghaosu), by Tu YY^[5], the new Lasker Debakey awardee, applied in malaria treatment which is considered to be one of the greatest achievements of integrative medicine has got worldwide consensus. Arsenic trioxide, another significant gift from integrative medicine, has been used in treating malignancies from the 18th to the 20th century. Over the past 30 years, arsenic was revived and shown to be able to induce complete remission and to achieve a 5-year overall survival of 90% in patients with acute promyelocytic leukaemia, when combined with all-trans retinoic acid and chemotherapy^[6]. In addition, it was also found to have some further improvements about arsenic trioxide on its molecular mechanisms^[7, 8] in fighting leukaemia.

As for CDs, to study the efficient ingredients of Chinese herbs is also a very popular probing direction. Ginsenoside Re^[9], a new research focus of integrative medicine, possesses the multifaceted beneficial effects on the cardiovascular system. It has a negative effect on cardiac contractility and autorhythmicity in alternations of cardiac electrophysiological properties and also exerts an anti-ischemic effect and induces angiogenic regeneration. The China Coronary Secondary Prevention Study^[10], the largest multi-centre, randomised and placebo-controlled study (involving in 4,870 patients), showed that Xuezhikang, a partially purified extract from fermented red yeast rice, significantly decreased the recurrence of coronary events and the occurrence of new cardiovascular events and improved lipoprotein profile. Moreover, it^[11] demonstrated that the Crataegus extract (WS 1442) could improve the exercise capacity of patients with heart failure and typical heart failure-related clinical symptoms. In a multi-centre^[12], randomised, double-blind, placebo-controlled trial of 335 patients, it was found that the administration of XS0601 (effective ingredients from Chuangxingol and paeoniflorin) for 6 months was associated with a

significant decrease in restenotic rate and recurrent angina in post-percutaneous coronary intervention (PCI) patients with acute coronary syndrome (ACS). A meta-analysis about the compound Salvia pellet^[13], consisting of active herbal ingredients extracted from Danshen (*Salvia miltiorrhiza*), San qi (*Panax notoginseng*) and Borneol (*Cinnamomum camphora*), has a significant effect on the improvement of angina symptoms and ELECTROCARDIOGRAM results with few adverse events in the treatment of stable angina pectoris. The *Panax quinquefolium* saponin^[14] (extracted from the stems and leaves of *Panax quinquefolium*) treatment significantly improves acute myocardial infarction-induced left ventricular remodelling and protects the myocardium against ischemia-reperfusion injury. Besides, the efficacy of coronary heart disease (CHD), the use of tetrandrine^[15] (extract from *Radix Stephaniae tetrandrae*) and tetramethylpyrazin (extract from *Rhizoma Chuanxiong*) was found to add effect on exercise tolerance and cardiac function for patients with connective tissue disease complicated with pulmonary arterial hypertension. Tetrandrine^[16] can significantly decrease the level of lipid peroxide and thromboxane B2, and distinctly increase the level of human superoxide dismutase-1 gene in cases of hypertensive patients. Tetrandrine can also simultaneously decrease BP, prevent atherosclerotic and thrombosis through blocking voltage-dependent calcium channel of vascular smooth muscle and myocardial cells. Moreover, berberine^[17], an alkaloid originally isolated from the Chinese herb Huang Lian (*Coptis chinensis*), has been found to lower cholesterol in hypercholesterolemic patients and up-regulate hepatic low-density lipoprotein receptor expression. And Xuezhikang^[18] has been shown to lower total cholesterol, low-density lipoprotein cholesterol and triglycerides and increase high-density lipoprotein cholesterol.

3.2 Combining therapies

Indeed, the use of integrative medicine in clinical practice is very common in China and some neighbouring countries. Besides, the significant finding that^[19] Oseltamivir and maxingshigan-yinqiaosan, alone and in combination, reduced time to fever resolution in patients with H1N1 influenza virus infection suggest its alternative value in the treatment of H1N1 influenza. In the field of CDs, it may be the most used among the number of studies conducted on CHD. The results^[20] showed that Tongxinluo dose-dependently enhances the stability of vulnerable plaques and prevents plaques from rupture. Simvastatin and Tongxinluo offer similar protection in terms of lipid-lowering, anti-inflammation and anti-oxidation. Recently^[21], our research group conducted a prospective, randomised, controlled, non-blinded, multi-centre trial on patients with ACS after PCI and found that treatment with CHM for nourishing *qi* and removing blood stasis in combination with WM was associated with a significant decrease in cardiovascular endpoint events in 1 year and the improvement in the quality of life with no increased risk of haemorrhage. Furthermore, the Liandouqingmai Recipe^[22] can raise the scores of the Seattle Angina Questionnaire and NO level and decline ET level in patients with CHD on the basis of conventional standard treatment, thus improving vascular

endothelial function and life quality. The meta-analysis^[23] of randomised, controlled trials for addition of CHM showed that it is very likely to be able to improve survival of myocardial infarction patients who are already receiving biomedicine. It^[24] also indicated a protective effect of integrating the use of Xiongshao capsule on restenosis and suggested that Xiongshao capsule may be used to prevent restenosis after a PCI procedure in CHD patients. In addition, it is worthwhile to mention that^[25] the qi-regulating, chest-relaxing and blood-activating therapy integrated with some Western medicines was adopted for syndrome X; the results showed that it can reduce the frequency and degree of angina, improve the symptoms and exercise the tolerance of patients, inhibit the inflammatory response of vascular walls and protect the function of vascular endothelial cells, which is better than that of the simple and conventional WM alone.

For cardiac heart failure (CHF), a systematic review of the observations of Shengmai^[26] also showed itself or plus WM treatment to be more beneficial for CHF compared to placebo or WM treatment alone. The Astragalus granule^[27] showed to be sufficient to display a beneficial effect on improving heart contraction at the moderate dose and a dose-dependent trend in improving the quality of life for patients with CHF. The application^[28] of invigorating *qi* and ascending *qi* therapy collapse based on routine WM therapy could suppress the chronic proliferation of myocardial collagen significantly, improve ventricular reconstruction and cardiac function and retard the occurrence and development of CHF to viral myocarditis through clinical observations. And Xinmailong^[29] was found to be more (almost double) statistically significant as compared with the available drug treatments for CHF. For the treatment of hypertension, combining compound Apocynum tablets^[30], Zhenjv pills and other antihypertensive drugs are also used widely for better clinical effects on hypertension. Danshen and Gegen adjunctive treatment^[31] was well tolerated and it significantly improved atherogenesis in high-risk hypertensive patients, with potential in primary atherosclerosis prevention. The meta-analysis^[32] indicated that biomedical treatment plus CHM is more effective than biomedical treatment alone in treating patients with dilated cardiomyopathy and heart failure.

3.3 Explaining WM finding by TCM theory

The TCM theory is very broad and profound. Generally, there are two ideological ideas that fully penetrate into the whole system. The first is the homeostasis idea that focuses on the integrity of human body and emphasizes^[33] the reflection of harmony^[34] between humans and nature, between the organ systems, tissues and vital substances of the body and between the mind and emotions. The second is the dynamic idea, self-controlled or internal balance, that stresses on the movement in the integral human body; people of different 'syndrome kind' have different characteristic clinical symptoms.

There^[35] was a manifest regulation of the pathological circadian rhythm of premature ventricular contractions in patients with viral myocarditis. The age of patients and concrete time in a day were all showed some relations with pathological rhythm. The circadian distributions of premature

ventricular contractions were variable in patients with different syndromes. Therefore, the theory of chronomedicine of TCM, which has been established under the guidance of the system view of the 'Correspondence between man and nature' and mainly studies on the relationship between disease and time, may be used to guide the treatment based on syndrome differentiation. In a polymorphism study^[36], ApoE epsilon4 allele as the risk factor of CHD, especially E3/4 genotype has a relatively close relationship with patients of phlegm syndrome. The pathogenesis of hypercholesterolemia^[37] is believed to involve the production of internal 'dampness' and 'phlegm' that leads to internal obstruction including 'qi stagnation' and 'blood stagnation'. The three main zang organs involved are believed to be the spleen, liver and kidney, though the heart is obviously involved by virtue of the fact that it controls the circulatory system.

Blood stasis^[38] is supposed to be a pivotal pathogenic mechanism of CHD in contemporary Chinese medicine. Now, it is making further thought about the presentation and pathology change in acute cardiovascular events of CHD. The toxin, including the unbalance caused by any internal or external factors or the combination and transformation of toxin and blood stasis of Chinese medicine, are involved in the pathogenesis of CHD according to the basic theory of Chinese medicine. And the 'Toxin'^[39] theory of CM has close similarity with the inflammation response theory in ACS.

Besides the above, there is also some innovation of the TCM theory in the studies of CDs treatment. Ancient TCM physicians^[40] basically share the same knowledge on vascular system with biomedicine in terms of its anatomical structure, but the distinctive TCM theory on qi-blood correlation can enrich the contents of the vascular system. It was brought forward, the conception of 'collateral-vascular system disease', to regulate the treatment of CDs.

4. ADVANTAGES OF INTEGRATIVE MEDICINE

Integrative medicine emphasizes the relationship between TCM and WM and tries to explore more effective methods for CDs. This treatment method seems complicated, but it has several obvious advantages: (1) it not only draws attention to the overall function of the body, but also emphasizes on target-orientation therapy; (2) it attaches importance to the combined effect of the multi-component and their interactions and (3) it provides evidence of dynamic pathological and physiological changes to make suitable adjustments. As a result, the integration medicine does well in increasing curative effects, reducing side effects and proving a new mechanism in the treatment of CDs.^[41, 42]

5. FUTURE PROSPECTS

With the development of modern biologically concentrated medicine such as sketch mapping genomic sequence, functional genomics, proteomics and pharmacogenetics, we now

have more advanced techniques for elucidating the possible complicated biological networks and complex pathophysiological mechanisms underlying integrative medicine. According to the biological relationship between genes and proteins, complexity of CDs mainly lies in the interactions of genes and its transcription proteins with each other. Therefore, it is a great challenge to obtain ideal results from an intervention on a single target for the CDs. Meanwhile, the intervention of WM to single target occasionally causes serious side effects and drug resistance.

According to the theory of TCM, the complex relationship in an organism is always a black box compared with the recognition ability of a human being, and it is necessary to explore the adaptation disciplinarian of human body to the biological information of nature (including food, drug and ecologic environment).^[43] Integrative medicine which brings the experience of TCM accumulated in thousands of years and the whole concept into its medical system will play a significant role in the treatment of CDs^[44, 45], which pushes us forward to the further study of the medical development of (1) finding some effective chemical components or ingredients and using integrative methods to treat CDs; (2) finding some new targets to treat CDs from molecular level such as gene^[46]; (3) elucidating some complex mechanism of CDs from the net regulation of gene and protein and (4) providing more treatment methods of integrative medicine that might improve long-term prognosis of CDs.

6. CONCLUSION

The significant improvement for treatment on CDs was made by using the integrative medicine approaches. However, there are still some challenges in the application of integrative medicine in the future: (1) unimaginably various and complicated ingredients of Chinese herbs waiting to be found; (2) the standardized quality control required to be improved for CHM; (3) potential interactions between WM and CHM to be investigated further; (4) large-scale, rigorously designed clinical trials still too limited, primary endpoints not used widely and (5) too much repetitive studies, more researching field to be explored. These are all encouraging us to do further study for the optimal medical service of CDs.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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