Clinical practice of traditional Chinese medicines for chronic heart failure

Shufei Fu,1 Junhua Zhang,1,2 Xiumei Gao,1 Ye Xia,1 Rita Ferrelli,3 Alice Fauci,3 Ranieri Guerra,3 Limin Hu1

ABSTRACT
Background Chinese medicines have been used for chronic heart failure (CHF) for thousands of years; however, the status of traditional Chinese medicines (TCMs) used for CHF has not been reported. This review was carried out in the framework of a joint Sino-Italian Laboratory.

Objective To investigate the baseline of clinical practice of TCMs for CHF, and to provide valuable information for research and clinical practice.

Methods The authors included articles about the use of TCMs for the treatment of CHF by searching the Chinese Journal Full-text Database (1994 to November 2007).

Results In all, 1029 papers were included, with 239 herbs retrieved from these. The most commonly used herbs included Huangqi (Radix Astragali), Fuling (Poria), Danshen (Radix Salviae Miltiorrhizae), Fuzi (Radix Aconiti Lateralis Preparata) and Tinglizi (Semen Lepidii). Modern Chinese patent medicines (produced by pharmaceutical companies) and traditional prescriptions (comprising several herbs) are the application forms of these drugs. Shenmai, Shengmai and Astragalus injections were the most commonly used Chinese patent medicines. Some classic prescriptions (including Zhenwu decoction, Shengmai powder and Lingguizhuang decoction) were also frequently used. The effectiveness and safety of the TCMs were both satisfactory, and the traditional Chinese medicine and western medicine therapy could significantly improve the clinical effectiveness and reduce some of the adverse reactions from western medicines used alone.

Conclusion The authors have acquired overall information about the clinical application of TCMs for CHF. Modern pharmacology has provided limited evidence for the rationality of this clinical use. Further research is needed to provide more evidence.

INTRODUCTION
Chronic heart failure (CHF) is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.1 Heart failure (HF) is the end stage of cardiac disease. The American Heart Association (AHA) Statistics Committee indicates: heart failure incidence approaches 10 per 1000 population after 65 years of age. The estimated direct and indirect cost of HF in the USA for 2006 is $34.8 billion.2

Over the past several decades, various types of drugs have been applied to treat CHF. Several have been proven effective to improve the syndromes of CHF, but usually patients show poor compliance because of adverse effects and especially for long-term use. In contrast, traditional Chinese medicines have certain advantages for the treatment of CHF, as they are multilevels multitargeted, and they have few side effects.3 However, the clinical application for CHF has not been systematically analysed. To investigate their clinical use and to gain valuable information for research and clinical practice, we carried out a comprehensive review.

RESULTS
Outcomes of selection of the literature
According to the search strategy, we obtained 4415 potentially relevant papers (see Figure 1). After selection according to the inclusion and exclusion criteria, 1029 papers were identified as directly relevant. Of these, 774 were controlled clinical trials (CCTs), 253 were case reports, and 22 were clinical
experience summaries. The total number of participants included in the 1029 studies was 77,691.

Clinical application of single Chinese herb
In all, 239 Chinese herbs were used in the 1029 papers. The drugs that had a frequency higher than 50 were Huangqi (Radix Astragali), Fuling (Poria), Danshen (Radix Salviae Miltiorrhiae), Fuzi (Radix Aconiti Lateralis Preparata) and Tongli (Semen Lepidii).

Thirty herbs with a frequency of more than 50 in which six herbs were documented as benefiting vital energy (Qi) and improving heart function, including Bai Zhu (Rhizoma Atractyloids Macrocephalae), Gancao (Radix Glycyrrhizae), and Renshen (Radix Ginseng), eight herbs were specifically related to the promotion of blood flow (Huo Xue) such as Danshen (Radix Salviae Miltiorrhiae), Chuanxiong (Rhizoma Chuanxiong) and Honghua (Flos Carthami). Seven herbs reduced water retention (Lishui), including Fuling (Poria), Guizhi (Ramulus Cinnamomi) and Zexie (Rhizoma Alismatis). Huangqi (Radix Astragali) had effects that not only benefited vital energy but also reduced water retention. Similarly, Yimucao (Herba Leonuri) could both promote blood flow and reduce water retention.

Clinical application of Chinese patent medicines
The Chinese patent medicines refer to some kinds of dosage form, based on the theory of TCM, and incorporating Chinese herbal medicine as raw material. They are produced under the guidance of the formula principle and the science technology. The commonly used formulations include pills, tablets, injections and capsules. Chinese patent medicines are characterised by their ease of administration and storage, and by their rapid onset of action and quality control.

Among the Chinese patent medicines for CHF, injections with Shenmai, Shenmai, Astragalus and Shenfu were used frequently (table 1).

Clinical application of traditional prescriptions of Chinese herbs
Traditional prescriptions of Chinese herbs can include a single Chinese herb or a number of herbs, depending on the premise of syndrome differentiation, according to the principle of the compatibility for the prescription. These prescriptions are characterised by the individualised treatments. Shenmai decoction, Shengmai preparations and Lingguizhuguan decoction were used frequently as the classic prescriptions for CHF (table 2).

Clinical application of TCMs combined with western medicines
Randomised controlled trials (RCTs) were recognised as the more valuable research design to access the efficacy and safety.

Table 1 Chinese patent medicines for chronic heart failure and their main components

<table>
<thead>
<tr>
<th>Name</th>
<th>Components (Latin name)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shenmai injection</td>
<td>Radix Ginseng Rubra, Raidox Ophiopogonis</td>
</tr>
<tr>
<td>Shengmai injection</td>
<td>Radix Ginseng Rubra, Raidox Ophiopogonis, Fructus Schisandrae</td>
</tr>
<tr>
<td>Astragalus injection</td>
<td>Radix Astragali</td>
</tr>
<tr>
<td>Shenfu injection</td>
<td>Radix Ginseng Rubra, Radix Aconiti Lateralis Preparata</td>
</tr>
<tr>
<td>Compound salvia injection</td>
<td>Radix Salviae Miltiorrhiae, Lignum Dalbergiae Odoriferae</td>
</tr>
<tr>
<td>Puerarin injection</td>
<td>Radix Puerariae</td>
</tr>
<tr>
<td>Salvia injection</td>
<td>Radix Salviae Miltiorrhiae</td>
</tr>
<tr>
<td>Wexin particles</td>
<td>Radix Codonopsis, Rhizoma Polygonati, Radix Seu Rhizoma Nardoatychos, Radix Notoginseng</td>
</tr>
<tr>
<td>Shenqifuzheng injection</td>
<td>Radix Codonopsis, Radix Astragali</td>
</tr>
<tr>
<td>Tongxinluo capsule</td>
<td>Radix Ginseng, Hirudo, Scrophula, Lignum Santali Albi, Eupolyphaga Scleroplea, Scolopendra, Olbanum, Peroniascum Cicadae, Lignum Dalbergiae Odoriferae, Radix Paeoniae Rubra, Semen Zuphi Spinoseae, Broneolum Synthenticum</td>
</tr>
</tbody>
</table>

Therefore, we further analysed 684 RCTs included in our study. Among these RCTs, 626 studies took effective rate as an evaluation index. Four hundred and forty-two RCTs with 59,081 participants (21,034 patients in treatment group) of the 626 RCTs used the conventional treatment based on the ACC/AHA 2005 guideline in control group. The conventional treatment mainly included the combined application of drugs such as angiotensin-converting enzyme inhibitors (ACEI), β-blockers, kinds of diuretics and digitalis. The interventions of the treatment group of the 442 studies were these conventional treatments plus TCMs. (The most commonly used TCMs are listed in tables 1, 2.)

We changed the three grades of ranked data into two grades (effective and invalid). The effective rate of treatment group was 91.08% (19,158 of 21,084) compared with 75.97% (15,349 of...
CHF has become a hot issue, receiving considerable attention by therapy or non-drug therapy with good efficacy and fewer adverse reactions. TCM-WM therapy could reduce mortality and improve the effective rate compared with western medicines used alone.

Analysis of potential adverse effects of the drugs based on the clinical trials

Adverse effects of the drugs based on the clinical trials were also analysed in our study. One hundred and eighty-six studies (18.08%) reported that no side effects occurred at the end of their treatment, and 706 studies (68.61%) did not mention any information on side effects. Another 137 studies with the patients of 12,063 reported the adverse reactions after the treatment. No treatment-related deaths were reported.

Table 3 Adverse reactions of patients using Chinese medicines alone

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>No</th>
<th>Treatment and outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea, vomiting/abdominal distension, diarrhoea</td>
<td>27</td>
<td>Short-term withdrawal that is better/improved with symptomatic treatment/improved with no special treatment</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>8</td>
<td>Short-term withdrawal that is better</td>
</tr>
<tr>
<td>Dry mouth/feverish dysphoria</td>
<td>10</td>
<td>Improved with no special treatment</td>
</tr>
</tbody>
</table>

We also found that TCM-WM therapy could significantly improve the clinical effectiveness and reduce some adverse reactions originating from western medicines used alone (listed in table 4).

In 2000, the USA, China, Australia and Thailand jointly carried out an international cooperation to investigate the prevalence and distributing features of Asian cardiovascular disease. A total of 15,518 adults were surveyed. The prevalence of CHF was 0.9%, and the rate increased substantially with ageing in China.7 To solve the problem in China, the major treatments for CHF were Chinese medicines and Western medicines used respectively or used together.

Currently, in China the application of western medicines for CHF mainly followed the guidelines of ESC3, ACC/AHA1 and the guidelines for the diagnosis and treatment of CHF in 20079 made by the Chinese medical association. These guidelines recommended the combination of cardiotoxic, diuretics and vasodilators.

Treatment with Chinese medicines for CHF can be traced back to 1000 years ago. The earliest records on prevention and treatment for CHF were found in the book written by Sun Simiao, a well-known ancient Chinese doctor.10 With time, TCMs have accumulated a wealth of experience to treat CHF. Many well-known classic prescriptions (listed in table 2) with the advantages of significant efficacy and fewer adverse reactions have been used to date. Also, Chinese patent medicines (listed in table 1) manufactured using modern pharmaceutical technology now apply widely as guaranteed safety, effectiveness and controllable quality. According to TCM theory, the commonly used Chinese medicines (single Chinese herb, Chinese patent medicines and traditional prescriptions) for CHF have effects that are beneficial for vital energy, promoting blood flow and reducing water retention.11

Currently in China, TCM-WM therapy for CHF is very popular. Four hundred and forty-two studies (64.62%) of the 684 RCTs used TCM-WM therapy in a treatment group. As for the principles of prescription compatibility based on TCM theory, the purpose of the TCM-WM therapy is also to maximise the advantages of the two kinds of therapies and reduce the incidence of adverse reactions.

This study has also analysed the controversial issue of adverse reactions in Chinese medicines. Chinese medicine injection applied in five of the 14 studies with Chinese medicine intervention used alone, which reported the side effects. Studies have shown that the incidence of adverse reactions to Chinese medicine injections will increase compared with oral preparations due to factors such as preparation process, transport and storage.12 Another major factor for the occurrence of adverse reaction is ignoring the drug’s instructions.13 Some ingredients found in Chinese herbal medicines were proved to be toxic. Therefore it was required reasonable compatibility to reduce the...
toxicity and adverse reactions. Taking Fuzi (Radix Aconiti Lateralis Preparata) as an example, its main ingredient is aconite alkaloids, whose effects include improving the myocardial contraction, dilation of blood vessels and increasing the blood flow. It is commonly used in the treatment for CHF such as the classic prescription Zhenwu Decoction and the Chinese patent medicine Shenfu injection. However, sometimes Fuzi may cause side effects such as nausea, vomiting, diarrhea or arrhythmia. The toxicity may decrease through reasonable prescription compatibility and application. Our study indicated that the adverse reactions of Chinese medicines used alone recovered easily through short-term withdrawal or simply symptomatic treatment.

In the ESC and ACC/AHA guidelines, commonly used medicines included diuretics (IA), ACEI (IA), B-blockers (IA), digitalis (IIa, A) and so on. However, significant efficacy accompanied adverse reactions, especially in long-term use. The usual adverse reactions of digitalis were arrhythmia, gastrointestinal symptoms (anorexia, nausea, vomiting) and nervous psychiatric symptoms (impairment of vision, disorientation, confusion). The Writing Committee of ACC/AHA changed the level of recommendation for digitalis glycosides from Class I to Class IIa, having considered the risk/benefit ratio.1 As one of the most popular medicines for CHF, the common adverse reaction of ACEI was dry cough, which became the reason for withdrawal. These side effects could be seen in the control group of RCTs with conventional western medicine intervention (listed in table 4). The incidence of the above adverse reactions decreased significantly after the Chinese medicines were added to the treatment group. This suggested that the therapy of TCM-WM under the principles of compatibility could reduce the occurrence of side effects.

Modern pharmacology research has provided limited evidence for the rationality of the clinical use of TCMs. It mainly focused on a few commonly used herbs. Several reports suggest that Huangqi extract (astragalus polysaccharides) can alleviate myocardial reperfusion injury.14 Also, purified Danshen (Radix Salviae Miltiorrhiae) extract has cardioprotective effects, which, at lower doses, could alleviate ischaemia-reperfusion injury.15 Tinglizi (Semen Lepidii) can decrease the total collagen content of the ventricle and attenuate ventricular remodelling induced by abdominal aortic banding.16 17 Modern pharmacological studies have shown that most of the herbs for CHF are able to improve heart function and promote blood circulation and diuresis.18

The quality of the methodology of the literatures included in our study was not high, and this affected the reliability of our results. In order to produce scientific evidence for the efficacy and safety of TCMs, high-quality clinical studies are needed. On the other hand, basic research is also important, to reveal the material basis and mechanisms of Chinese medicines by using modern drug research technologies including phytochemistry, pharmacology, toxicology, molecular biology, cell biology and metabolomics.

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