

EDITORIAL COMMENT

Cardiotonic Modulation in Heart Failure

Insights From Traditional Chinese Medicine*

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Medicinal herbs have been used over the past centuries for restoring the body's homeostatic balance. Contemporary use of herbal supplements remains widespread in many cultures as treatment for specific ailments. Many possess cardiovascular actions, and some interact with cardiac medications. However, there is variable scientific evidence with respect to their safety and efficacy, and few have been subjected to the same rigorous evaluation processes and regulations as contemporary pharmaceuticals (1). In the field of heart failure, we have also witnessed the failure of promising naturopathic therapies like hawthorn extract in translating their potential benefits in rigorous clinical trials (2,3).

See page 1065

In traditional Chinese medicine (TCM), the heart is the home of spirit or mind (*shen*). The heart *qi* is the power for blood circulation and keeps blood in the vessels, whereas heart *yang* can warm organs and promote fluid metabolism. The fundamental problem in heart failure is the prolonged deficiency of heart *qi* and *yang*, which causes the heart to become too weak to move blood and transport fluid, leading to blood “stasis” and excessive fluid retention (4). These pathological factors can influence each other and present different symptom patterns. Hence, the treatment principles are that they collectively invigorate the heart *qi* and warm *yang*—specifically by accelerating blood circulation, liberating flow of the network vessels, disinhibiting water, and dispersing swelling. These theories mirror the

classic cardiocirculatory model of heart failure in Western medicine, although their physiological effects may be difficult to quantify. Regardless, few TCM remedies for heart failure have been put into scientifically rigorous clinical evaluation, and their users are largely confined to strong believers in TCM.

In this issue of the *Journal*, Li et al. (5) reported the results of a double-blind, multicenter, placebo-controlled, prospective, randomized clinical trial of qili qiangxin capsules in more than 500 patients with systolic heart failure. Qili qiangxin is a formulation based on several common medicinal herbs in TCM that are well known to have cardiotonic and immunomodulatory effects (6–8). Combined in a capsule form, some herbs are commonly used in many Chinese households for everyday food preparations. The researchers reported an approximately 25% reduction in N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and a greater proportion of patients with $\geq 30\%$ reduction in NT-proBNP levels after 12 weeks of qili qiangxin capsules compared with placebo (5). These findings paralleled the improvements in New York Heart Association functional class, quality of life scores, and left ventricular ejection fraction (LVEF) observed in the treatment group—all without incremental adverse events (5).

Because few pharmacological therapeutics have crossed the threshold in delivering much-needed breakthroughs in the field of heart failure over the past decades, the investigators should be congratulated for conducting a rigorous clinical trial that encompasses all of the elements of an objective scientific evaluation of this TCM patent drug. It is also reassuring that no substantial harm was observed in this relatively large sample size, even though the exposure duration was relatively short (12 weeks). Clearly, larger validation studies are needed to provide further evidence for its use, particularly with a broader investigational community. However, the most obvious question to reconcile is how a relatively modest (albeit statistically significant) short-term improvement in LVEF in the absence of a significant change in overall left ventricular dimension can translate into potential long-term benefits of qili qiangxin. Perhaps the answer lies in the search for the active ingredients of qili qiangxin. With contemporary mass spectrometry approaches, a broad range of organic compounds such as triterpenoid saponins, flavonoid glycosides, C21-steroids, and phenolic acids can be identified in qili qiangxin capsules (9). Ginsenosides, often found in ginseng, may modulate the Na^+/K^+ -ATPase channels, thereby explaining the “cardiotonic” properties similar to those found in many conventional remedies, including digitalis (10). This is an important cautionary note because several promising drugs with cardiotonic or metabolic modulation as their pharmacodynamic profile have emerged over the past decades but did not demonstrate incremental benefits. For example, treatment with enoximone produced minimal changes in cardiac dimensions despite substantial improvements in LVEF and quality of life (11,12), and enoximone did not demonstrate

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morbidity or mortality benefits when studied in prospective, event-driven clinical trials (13).

Another potential insight from the report is the fact that the study population was composed of largely nonischemic but symptomatic and well-treated patients (with a mean 6-min walk distance comparable to that in mild to moderate heart failure). They were relatively young, with few comorbid conditions (creatinine: ≤ 2.2 mg/dl), and this was consistent with the fact that these patients had a relatively low event rate ($< 10\%$ annualized mortality rate and low heart failure hospitalization rate) and relatively preserved systolic blood pressure (mean: > 120 mm Hg). Nevertheless, the majority of patients were taking diuretic therapy with a rather high baseline NT-proBNP level (median: 1,815 pg/ml). It is therefore conceivable that additional decongestive (diuretic and/or natriuretic) effects of qili qiangxin may in part account for the observed reduction in NT-proBNP levels and improvements in morbidity. Unfortunately, we simply had too limited information about the background drug regimen for the study population—besides being stable for at least 2 weeks and whether or not dosing of background drugs had been modified during the study period—to draw any speculations.

We often struggle when faced with new ideas and new concepts from century-old holistic approaches. Regardless of the underlying mechanistic underpinnings, the most important task is to demonstrate that the approach provides incremental benefits and to learn how to best mitigate the risks. As Sir William Withering cautioned us from his infamous *Account of the Foxglove*, "... it is better the world should derive some information, however imperfect, from my experience, than that the lives of men should be hazarded by its unguarded exhibition, or that a medicine of so much efficacy should be condemned and rejected as dangerous and unmanageable" (10). The findings reported by Li et al. (5) have certainly given us much-needed information to derive some confidence and may have broken the barrier in establishing clinical evidence, which few TCM drugs have been able to accomplish. We can no longer put this therapeutic approach in the category of testimonial recommendation, even though it is obvious that much more long-term validation data are required. That being said, the relative concentrations of these ingredients are largely unknown, even when analyzed with the latest technologies. Also, like many similar TCM patent drugs, the "active ingredients" may not be as consistent from one capsule to another (14). Hence, the struggle with the lack of familiarity and unknown consistency of the active compounds in qili qiangxin capsules will likely remain the reasons why the results of this study may be received with cautious optimism. Above all, the use of a "pre-mix" patent drug like qili qiangxin is in direct conflict with the conventional reductionist approach of Western medicine, which requires the identification and isolation of the ingredients that provide the therapeutic efficacies. It is conceivable that, in the future, if qili qiangxin

proves to provide morbidity and mortality benefits in rigorous clinical trials, it will fundamentally challenge the existing foundation of scientific inquiry based upon the precise understanding of pharmacodynamics of drug therapies. Yet, even at present, the promising results reported by Li et al. may have opened the opportunity to explore with the latest technologies how synergistic interactions among active TCM ingredients can benefit the syndrome of heart failure. This is a challenge that we should all warmly embrace.

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