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Machine-readable Yin–Yang imbalance: traditional Chinese medicine syndrome computer modeling based on three-dimensional noninvasive cardiac electrophysiology imaging

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Abstract

Objectives: The principal diagnostic methods of traditional Chinese medicine (TCM) are inspection, auscultation and olfaction, inquiry, and pulse-taking. Treatment by syndrome differentiation is likely to be subjective. This study was designed to provide a basic theory for TCM diagnosis and establish an objective means of evaluating the correctness of syndrome differentiation.

Methods: We herein provide the basic theory of TCM syndrome computer modeling based on a noninvasive cardiac electrophysiology imaging technique. Noninvasive cardiac electrophysiology imaging records the heart's electrical activity from hundreds of electrodes on the patient's torso surface and therefore provides much more information than 12-lead electrocardiography. Through mathematical reconstruction algorithm calculations, the reconstructed heart model is a machine-readable description of the underlying mathematical physics model that reveals the detailed three-dimensional (3D) electrophysiological activity of the heart.

Results: From part of the simulation results, the imaged 3D cardiac electrical source provides dynamic information regarding the heart's electrical activity at any given location within the 3D myocardium.

Conclusions: This noninvasive cardiac electrophysiology imaging method is suitable for translating TCM syndromes into a computable format of the underlying mathematical physics model to

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offer TCM diagnosis evidence-based standards for ensuring correct evaluation and rigorous, scientific data for demonstrating its efficacy.

Keywords
Cardiac electrophysiology imaging, traditional Chinese medicine, forward problem, inverse problem, computer modeling, Yin, Yang

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Introduction

The fields of traditional and complementary medicine are important but often underestimated parts of health care. While traditional medicine has a long history of use in health maintenance and disease prevention and treatment, particularly for chronic disease[1–6] such as cardiovascular disease and cancer, rigorous scientific data are needed to demonstrate its efficacy and evidence-based standards for quality and safety evaluation.[7] The principal techniques of traditional Chinese medicine (TCM) are the four diagnostic methods of inspection, auscultation and olfaction, inquiry, and pulse-taking. Treatment by syndrome differentiation is therefore likely to be subjective. The eight general principles used in TCM to describe patients' conditions are Yin, Yang, exterior, interior, cold, heat, deficiency, and excess. Among these eight principles, Yin and Yang[8–11] are regarded as those that guide TCM syndrome differentiation. Accurate syndrome differentiation and proper treatment are the prerequisites for achieving good outcomes. However, syndrome differentiation is often inaccurate; for example, hyperglycemia caused by pathogenic damp attacking the spleen may be diagnosed as deficiency of Yin,[12] and diseases caused by Yang deficiency may be treated as Yang excess after the doctor's careful examination.[13] Thus, an objective means of evaluating the correctness of syndrome differentiation in TCM is urgently needed.

The author of an ancient Chinese medical text called *The Yellow Emperor's Inner Canon*[14] and his following medical men stated that the "heart is a monarch organ." The heart is undeniably one of the most important organs in the body. Reduction of cardiovascular disease even reduces the incidence of cancer. Consciousness, thinking, memory, and sleep are all related to the function of the heart. With respect to physiological functions, the heart is considered to be a muscular pump with rhythmic electrical activity and muscle contraction that expels blood to all parts of the body. Thus, knowledge of the electrical function of the heart can be a critical tool with which to attain a scientific understanding of TCM syndromes. Fortunately, significant progress has been made in the field of cardiac electrophysiology with respect to recording the electrical activity of the heart. For example, standard 12-lead electrocardiography (ECG) is widely used in the clinical setting to record atrial and ventricular depolarization and repolarization. Moreover, the CARTO System (Biosense Webster, Irvine, CA, USA) and the EnSite System (St. Jude Medical, Saint Paul, MN, USA) are commercially available systems that provide endocardial electrical information.

However, because of the limited number of recording electrodes, 12-lead ECG does not provide spatial details of cardiac activation. Although the CARTO System and EnSite System more effectively characterize the heart's electrical activities, both systems are invasive.

To overcome the disadvantages of the above methods, noninvasive cardiac electrophysiology imaging[15] has been investigated by researchers. Noninvasive cardiac electrophysiology imaging records the heart's electrical activity from hundreds of electrodes placed on the surface of the patient's torso and therefore provides much more information than a 12-lead ECG recording. Through mathematical calculation of reconstruction algorithms, the reconstructed heart model is a machine-readable description of the underlying mathematical physics model. It reveals the detailed three-dimensional (3D) electrophysiological activity of the heart (including location, magnitude, and trend).

This approach has been clinically applied to assist in the diagnosis of cardiac abnormalities,[15–29] but it has not been used in TCM to date. In TCM, the imbalance between Yin and Yang is considered the root cause of a disease. Elucidation of the physical background of a traditional diagnosis in relation to Yin and Yang is clinically meaningful. Yang is associated with qualities such as heat, movement, activity, and light, while Yin is associated with qualities such as cold, rest, passivity, and darkness. More concretely, Yang excess results in heat syndrome while Yin excess leads to cold syndrome, and Yang deficiency causes cold syndrome whereas Yin deficiency induces heat syndrome. According to the Nernst equation (1), the electrical gradient across the cell membrane that prevents the net diffusion of an ion can be changed by temperature; thus, the imbalance between Yin and Yang is probably reflected by altered cardiac electrical activation. A definite relationship might exist between Yin–Yang imbalance and cardiac electrical activity. The Nernst equation is as follows:

$$V = -\frac{RT}{zF} \mathrm{In} \frac{C_i}{C_o} \qquad (1)$$

where V is the membrane potential, R is the gas constant, T is the absolute temperature, z is the valence of the ion, F is the Faraday constant, and C_o and C_i are the concentrations of the ion outside and inside the cell, respectively.

We herein present the basic theory of TCM syndrome computer modeling based on noninvasive cardiac imaging to allow for visualization of the most basic TCM syndromes (Yang excess, Yin excess, Yang deficiency, Yin deficiency, and lack of both Yin and Yang). Because correct syndrome identification is the premise and foundation of treatment in TCM, examination of the correctness of syndrome differentiation with assistance of TCM syndrome computer models derived from noninvasive cardiac electrophysiology imaging has broad clinical value in cardiovascular disease prevention and treatment.

Methods

Three-dimensional cardiac electrophysiology imaging is a novel noninvasive imaging modality that allows for visualization of the cardiac activity of the entire heart from body surface potentials measured with hundreds of electrodes together with heart–torso anatomic information obtained from computed tomography or magnetic resonance imaging scans. The ECG signals from hundreds of leads, which record much more information than 12-lead ECG, are used to noninvasively reconstruct the heart's electrical activity through ECG forward problem and ECG inverse problem calculation. Variations in torso shape, heart size and location, and internal inhomogeneities might influence the imaging results.

To solve the ECG inverse problem, a model of the forward problem is required. The ECG forward problem involves calculation of the body surface potentials from equivalent cardiac sources using the Maxwell equations:[30]

$$\frac{\partial(\mu H)}{\partial t} + \nabla \times E = 0 \qquad (2)$$

and

$$\frac{\partial(\varepsilon E)}{\partial t} + \nabla \times H = -J \qquad (3)$$

where **E** is the electric field, **H** is the magnetizing field, ε is the electric permittivity relating the electric flux density to the electric field intensity, and μ is the magnetic permeability relating the magnetic flux density to the magnetic field intensity.

The matrix describing the relationship between cardiac electrical activity and body surface potentials is referred to as the transfer matrix. A finite difference analysis model, which is partly described in our previous paper,[31] is chosen to numerically solve the ECG forward problem and obtain the transfer matrix. The transfer matrix obtained from forward problem computation is then used in ECG inverse problem calculation to noninvasively reconstruct the cardiac activity.

The ECG inverse problem involves determination of the electrophysiological information of the heart source from the measured body surface potentials, which are recorded via an array of electrodes placed on the patient's body surface to measure the difference in electrical potential during impulse propagation. The mathematical equation is represented as follows:[15]

$$AX(t) = V(t) \qquad (4)$$

where A is the transfer matrix from the cardiac equivalent sources to the body surface potentials in a given torso volume conductor, V is the vector of the measured body surface potentials at one sampling instant t, and X is the vector containing the unknown parameters of the cardiac inverse solution at t.

The ECG signals from hundreds of leads are used to reconstruct the heart's electrical activity based on the transfer matrix obtained from forward problem calculation. In the ECG inverse problem, the number of surface leads is generally still smaller than the number of variables; some techniques used to obtain unique solutions were discussed in our previous papers.[32,33] This reconstructed heart model is able to reveal the complex electrical system of the whole heart in more detail and thereby provide a reliable basis for treatment in a noninvasive way. For example, it can locate the region of arrhythmic activity in the heart. Thus, we plan to use this technique for TCM syndrome computer modeling in our study, which is described below.

TCM syndrome computer modeling of heart palpitation

Research plans

This multicenter, large-scale, long-term prospective study will be carried out to develop machine-readable TCM syndromes of heart palpitation. Although palpitation is usually benign, it is potentially life-threatening. A full description of the experiment in the form of a technology roadmap is shown in Figure 1.

A total of 50,000 patients with newly diagnosed heart palpitation will be enrolled to ensure that statistically significant results

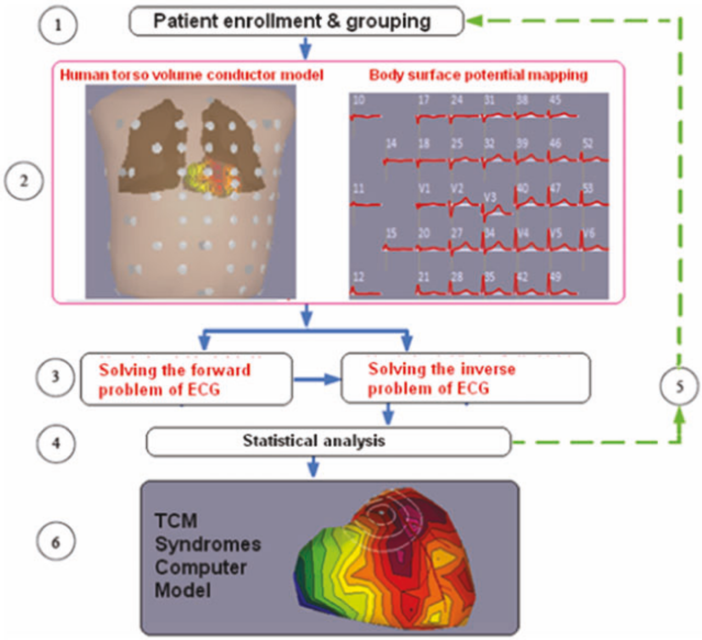

Figure 1. Technology roadmap showing the research steps of TCM syndrome computer modeling based on 3D noninvasive cardiac electrophysiological imaging. TCM, traditional Chinese medicine; ECG, electrocardiography.

are obtained. The inclusion criteria are as follows:

1. Male or female patients aged >18 years
2. Patients with a definitive clinical diagnosis of heart palpitations

The exclusion criteria are as follows:

1. Age of <18 or >75 years
2. Patients with a history of major neuropsychiatric disorder
3. Pregnancy or within 6 months of delivery
4. Unable or unwilling to comply with the study protocol

After all patients undergo inspection, auscultation and olfaction, inquiry, and pulse-taking, they will be divided into 5 groups (10,000 patients in each group) according the differentiation results from the TCM diagnostic techniques. The five groups represent five different syndromes: Yang excess, Yin excess, Yang deficiency, Yin deficiency, and lack of both Yin and Yang. The baseline data of the participants will be summarized using the form shown in Table 1.

Body surface electrical data of all patients will be acquired using a body surface potential mapping system, and magnetic resonance imaging scans will be performed to obtain a human torso volume conductor model of the patients. The body surface potentials and heart–torso geometric information will then be combined using imaging software to calculate the ECG forward problem and inverse problem, allowing for reconstruction of the dynamic cardiac electrophysiology throughout the entire 3D volume of the heart for all patients.

Table 1. Baseline data of the participants.

Patient number	Name	Sex	Age	Height	Weight
Inspection	Vitality:				
	Complexion:				
	Tongue coating:				
	Body (head, neck, five sense organs...):				
Auscultation and olfaction	Auscultation:				
	Olfaction:				
Inquiry	Chills and fever:				
	Perspiration:				
	Diet and appetite:				
	Defecation and urination:				
	Pain:				
	Sleep:				
	Life history, family history, occupation...:				
Pulse condition	Left hand	Cun:			
		Guan:			
		Chi:			
	Right hand	Cun:			
		Guan:			
		Chi:			
TCM syndrome differentiation					
Electrocardiography					
Echocardiography assessment					

Four consecutive heartbeats will be reconstructed and analyzed for each patient. The whole-heart model will be divided into 36 regions (apical, mid, and basal segments of the anterior, lateral, and inferior regions of both atria and ventricles). The activation time, recovery time, and QRST integral will be analyzed within each region, and comparisons between groups will be performed to identify the main differences and similarities.

Validation

The reconstructed whole-heart model computed by 3D noninvasive imaging of cardiac electrophysiology provides information regarding electrical depolarization and repolarization of myofibers at different sites and in different time periods; it includes the magnitude and direction of the current at any given location and every time instant. The simulation results of noninvasive imaging will be compared with those from invasive endocardial mapping systems such as the EnSite System and the CARTO System as part of the validation process.

Vectorcardiography is generally considered superior to standard ECG with respect to its diagnostic and prognostic value. Of the three major limited lead systems,[34–36] the vectorcardiogram derived via Kors' regression-related transformation is generally accepted as the best approximation. To assess the diagnostic and predictive abilities of our proposed method, the Kors-derived vectorcardiogram will also be used for multiple comparisons.

Sample size and patient recruitment

Determination of the sample size required to achieve a significant result is a key consideration in this study. Because we lack sufficient prior information regarding syndrome differentiation and treatment effects, a large number of participants needs to be enrolled to provide statistically reliable results. Additionally, if all of the developed algorithms for comparison of the heart models will be verified in Step 5 using new patients' data as shown in Figure 1, the number of patients required in this study will be relatively large. For these reasons, our target sample size is 50,000.

Patients will be recruited from Chinese tertiary hospitals and one German hospital. Recruitment of enough patients without delays lasting several years is critical in this study. The contingency activities (including initiating backup hospitals and launching advertisements) are well planned to ensure that a sufficient number of patients will eventually be included.

Clinical relevance

Chen et al.[37] showed that Western medicine combined with Chinese medicine based on syndrome differentiation provided more effective treatment than Western medicine alone. It not only reduced systolic blood pressure but also improved diastolic blood pressure, which might lower the incidence of cardiovascular and cerebrovascular events. Han et al.[38] reported that Chinese medicinals with properties of warming Yang and benefiting Qi had a significant effect on improving the left ventricular ejection fraction in rats with heart failure. Samuels et al.[39] evaluated the effect of the botanical compound Lcs101 on breast cancer. A study by Javid et al.[40] suggests that supplementation with the herbal medicine *Melissa officinalis* may improve the ejection fraction, maximum workload, cardiovascular serum biomarkers, and blood pressure in patients with chronic stable angina. Özdemir et al.[41] found that *Origanum onites* distillate had beneficial effects on lipid profiles, antioxidant status, and flow- and nitroglycerine-mediated dilatation of the brachial artery in patients with mild hyperlipidemia. Heart failure with a preserved ejection fraction can be attributed to palpitation, thoracic obstruction, edema, or other conditions according to its clinical manifestations. Ventricular remodeling is the inherent factor involved in the latent syndrome of heart failure, which is closely associated with blood stasis, and Yin asthenia can cause blood stasis, leading to the inability of heart Qi to promote the normal operation of blood in the vessel because of inadequate amounts of heart Qi and heart Yin. The main treatment of heart failure with a preserved ejection fraction is replenishing Qi and nourishing Yin.[42]

Diagnosis and treatment in TCM are mainly based on syndrome differentiation. Multidisciplinary computational modeling approaches[43–48] have become valuable tools for diagnosis, therapy, and prevention of diseases in the clinical setting, but these tools have not been used in TCM syndrome differentiation to date. Because correct syndrome differentiation is fundamental for effective treatment of diseases, this project is being performed to develop an application-oriented, machine-readable TCM Yin–Yang syndrome computer modeling system for cardiovascular disease with the aid of a noninvasive cardiac electrophysiology imaging technique. The TCM syndrome computer modeling system for heart palpitation will be established in combination with a computational electrodynamics technique, signal processing, and statistical analysis to allow for visualization of the most basic TCM syndromes: Yang excess, Yin excess, Yang deficiency, and Yin deficiency. The following two important topics will be studied in this project: reconstruction of a cardiac electrophysiology space–time model of healthy people and of patients with cardiovascular disease; and development of dynamic classification algorithms to compare the heart models in different time periods. All of the proposed approaches will be verified by large-scale patient-based research.

Discussion

In the herein-described study, we will generalize five cardiac electrophysiological computer models corresponding to the five TCM syndromes of palpitation, thereby providing a machine-readable and objective basis for identifying the TCM syndromes of heart disease.

Although the organs have different physiological functions, they are all connected by meridians involved in the circulation of blood and Qi,[49,50] which is one of the fundamental substances that maintains life activities. This is the holistic concept in TCM. In TCM, the heart is a "monarch organ" in the unity of the human body. The heart, consisting of heart Yin and heart Yang, is thought to dominate blood. Under the impulse of heart Qi, blood is transported throughout the whole body, providing nutrients to and removing waste products from the tissues. The sufficiency or insufficiency of Qi and blood can affect the heart's electrical activity. Thus, the herein-described noninvasive cardiac electrophysiology imaging method is suitable for translating TCM syndromes into a computable format of the underlying mathematical physics model to offer evidence-based standards for ensuring correct evaluation of TCM diagnoses and rigorous, scientific data for demonstrating its efficacy. Although malfunction of other organs can also cause Yin–Yang imbalance, this imbalance would be reflected in the cardiac electrical activity. Thus, a specific electrophysiological condition of the heart could lead to a specific Yin–Yang diagnosis, which would in turn suggest a specific cardiac condition.

Two important themes in clinical TCM are "treating the same disease with different therapies" and "treating different diseases with the same therapy." Thus, the present technique may have general implications in

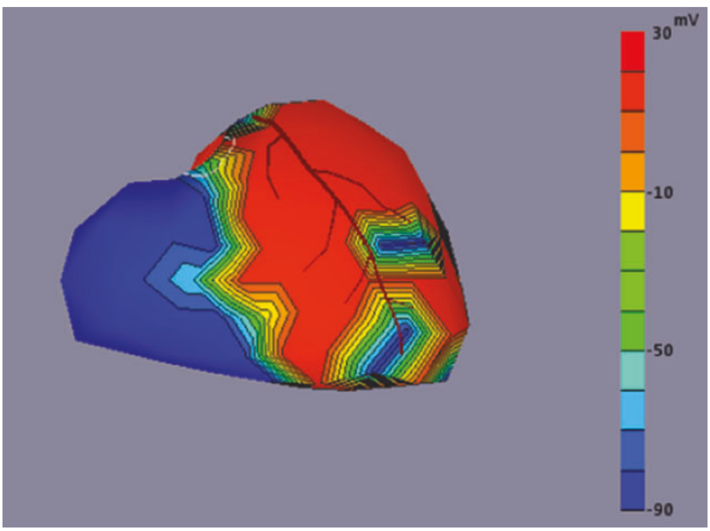

Figure 2. Reconstructed whole-heart model computed by three-dimensional noninvasive imaging of cardiac electrophysiology.

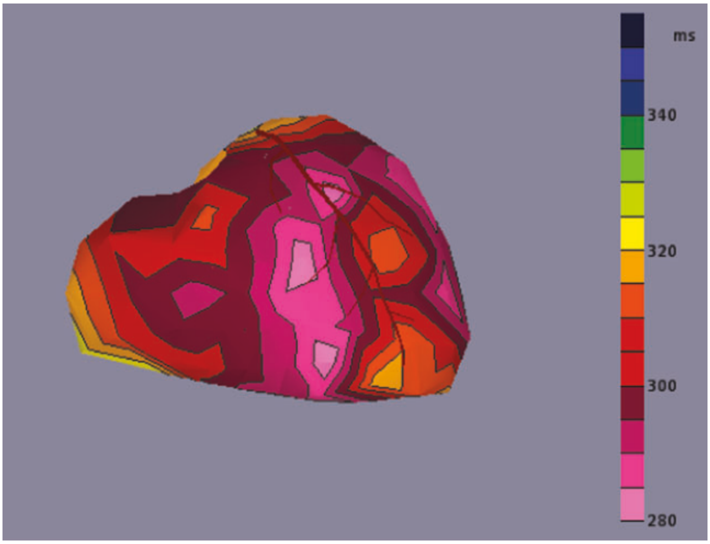

Figure 3. Reconstructed whole-heart model.

describing and diagnosing diseases—not only palpitation but also other cardiovascular diseases such as thoracic obstruction, angina pectoris, and asthma. Furthermore, cardiac electrical activity at different levels can be modified by medications; therefore, the method can be applied not only to examine the correctness of syndrome differentiation for disease treatment but also to quantify the effect of TCM prescription.

Hypothetically, because the balance in the autonomic nervous system is probably strongly related to Yin and Yang (Yin is perhaps parasympathetic and Yang is perhaps sympathetic), our proposed method might also be suitable for modeling and describing the function of the autonomic nervous system.

Figures 2 and 3 depict part of the simulation results. The imaged 3D cardiac electrical source can provide dynamic information of the heart's electrical activity at any given location within the 3D myocardium.

In this paper, we propose a methodological framework to develop computer models of Yin and Yang, which are basic concepts in TCM. Noninvasive 3D cardiac electrophysiology imaging was used to integrate TCM and Western medicine toward the development of computer modeling of TCM syndromes in the field of cardiovascular disease. Temperature changes have drastic effects on the cardiovascular system. Because Yin excess causes cold syndrome and Yang excess leads to heat syndrome, the five basic syndromes are expected to partially reflect the dynamics of temperature-induced changes in cardiac electrical activity. The final step of applying the electrical data to create a machine-readable TCM model for palpitation will not be described with actual data in our forthcoming study. Considerably greater specificity in this step, coupled with our preliminary experimental results, will be given in a future large-scale patient-based study. This study is being performed to lay the foundation for TCM digitalization, provide an objective means by which to evaluate the correctness of TCM syndrome differentiation, quantify the effect of TCM prescription to avoid misdiagnosis and inappropriate treatment as early as possible, and explore the modern scientific basis behind TCM theory of treatment by differentiating syndromes.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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