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REVIEW ARTICLE

Development of a Modern Pulse Diagnosis Using Harmonics Analysis of Arterial Signals

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ABSTRACT

Chinese medicine was proven to be clinically effective for thousands of years, and more and more studies have been conducted to confirm the impact of Chinese medicine in clinical practice. Pulse examination is a unique method of diagnosis in traditional Chinese medicine. However, there are still many opinions on how pulse diagnosis responds to physiological changes. Prof. Wei-Kung Wang and Prof. Yuh-Ying Lin Wang proposed the radial resonance theory, which suggests that blood is driven into the tissues by arterial pressure waves. The cardiac output produced the harmonics of the heartbeat, and the matching interaction of the heart and arterial system generated the harmonics of the pulse wave. In this study, we review the research on pulse diagnosis over the past three decades, outlining the development of theoretical models of pulse diagnosis, and the validation of physical and animal experiments with clinical studies and applications. We further attach the theory of arterial circulation resonance to wearable devices using harmonic frequency analysis for clinical disease research and prediction. The results of these studies provide evidence of the hemodynamic aspects of Chinese medicine, illustrating the possible mechanisms of Chinese medicine theory in modern physiology and the principles of Chinese herbal formula composition. Some conclusions and recommendations on how to systematize pulse diagnosis in Chinese medicine are also presented.

1. INTRODUCTION

Chinese culture has a long history, especially traditional Chinese medicine (TCM) has been clinically proven for thousands of years, and more and more studies have been conducted to prove the effectiveness of TCM in clinical practice. Sensing the pulse is a unique method of diagnosis in TCM, and Chinese medical books have richly documented pulse diagnosis for thousands of years. However, the pulse classification in the medical book is only described qualitatively, and the doctor must feel the pressure changes on the patient's radial artery at the wrist through the fingers to figure out and comprehend [1]. Although the text in the book depicts the pressure waveform changes felt under the fingers vividly, the actual application in clinical diagnosis is difficult to become an objective criterion for the different sensations and understanding of each TCM practitioner for different pulses. In order to make pulse diagnosis fit the development of modern medicine, we must systematically construct theoretical models, develop tools that can be used for formalized measurement, and carry out imitation, animal, and clinical experiments in order to transform TCM pulse diagnosis from qualitative descriptions in ancient books into indicators that can be repeatedly verified before we have a chance to bring TCM back into modern mainstream medicine.

TCM is based on a holistic perspective, treating the body as a black box system. By inputting stimuli (emotions, pathogenic factors, diet, etc.) and observing output evidence (inspection, listening and smelling, inquiry, and pulse diagnosis), TCM summarizes the main abstract changes in the system – changes in the functions of meridians and internal organs. On the contrary, modern medicine adopts a very different approach in analyzing the physiological system of the human body: by continuously dividing the system into layers, the human body is divided into several systems, such as neurological, circulatory, endocrine,

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digestive, and immune systems; the system layer is divided into different organs; the organ layer is divided into tissues; the tissue layer is divided into cells; the cell layer is divided into various organelles; and the organelles are operated by various chemical molecules. This is a very detailed approach to research. The advantage is that we have a clear understanding of each part of the system, but the disadvantage is that the interactions between the systems are unclear. In the case of the circulation system, the heart is considered as a pump that injects blood into the blood vessels and delivers it to the tissues through the blood vessels like a water supply [2]. Since 1628, Harvey proposed that the human cardiovascular system operates in a circulatory manner. The modern medical discussion of hemodynamics began with the analysis of the flow of a small piece of blood in the aorta, and many equations of fluid mechanics were developed, such as the Navier-stoke equation [2]. These equations were then used to understand the physiological operation in order to predict relevant pathologies or treatment patterns. However, so far, only some local changes or reactions of blood vessels can be explained. For related circulatory diseases, such as cardiovascular diseases, hypertension, and some basic physiological phenomena such as the existence of diastolic blood pressure, the position of the heart, and the curvature of the main ascending artery, the causes and solutions are still not available, and there is plenty of room for improvement.

For the circulation system, blood pressure measurement to arterial pressure waveform analysis has been developed for more than 100 years to monitor and study cardiovascular diseases [2]. In the beginning, the analysis of blood pressure data only quantified the highest and lowest points of the arterial pressure waveforms to assess the association between systolic pressure [3], diastolic pressure [4], and the occurrence of cardiovascular diseases. After accumulating sufficient clinical data, Staessen et al. used statistical models and regression analysis in hypertension studies and found that the magnitude of pulse pressure (systolic-diastolic) could also be used as a risk factor to assess total mortality [5]. In the last two decades, an emerging research method has been used to measure arterial pressure waveforms at one to two locations and extract the features through the turning points in the time domain. The pulse wave velocity and the Augmentation index are calculated and can be used as indicators of vascular sclerosis. These two indices are frequently used in studies of aging [6,7], hypertension [8,9], coronary artery disease [10,11], and renal disease [12,13]. In addition to the time domain analysis, there are also studies to obtain the proportional relationship between the harmonics of arterial pressure waves in the arm artery, wrist artery and carotid artery by frequency domain analysis, and then obtain the commonly used transfer function [14,15]. By using the transfer function, the arterial pressure waveforms of the radial wrist artery and arm artery can be more conveniently reconstructed back to the arterial pressure waveform of the carotid artery to estimate the real arterial pressure waveform closer to the aorta. However, the arterial pressure waveform extracted from the time domain is not sufficient to present the complete information of all arterial pressure waves. The harmonic analysis is a feasible tool for the complete response of the arterial pressure waveform [2]. Based on the mentioned physiological phenomena, Prof. Wang Wei-Kung and Prof. Lin Wang Yu-Ying believe that the current circulation theory will be stifled to explain the circulation system. Therefore, the radial resonance theory was proposed to explain the phenomena of such a complex system by simple physics [16–20]. The major difference between the radial resonance theory and the conventional flow theory is that the radial resonance theory suggests that the circulation system transmits energy by pressure rather than by flow. In this study, we have selected 59 representative papers from 110 related papers. The criteria used were whether they were peer-reviewed, reproducible, and accessibility. The physical and mathematical modeling of radial resonance theory, physical simulation experiments, frequency response studies in animal organs, and clinical applications in various related fields are summarized.

2. BIOPHYSICAL MODELING AND HARMONIC ANALYSIS

In the study of organ frequency response, Prof. Wei-Kung Wang discovered the resonance phenomenon between the viscera and the arteries [21]. Therefore, Prof. Wang and Prof. Lin collaborated on the derivation of the fluctuation equation of the arterial system and developed the theory of pressure-radius wave (PR wave) fluctuation to explain the basis of pressure fluctuation in the arteries, and proposed a novel hemodynamic model to explain the interaction behavior of the ventricle and the arterial system [22–25]. In this combined cardiac and aortic system, the eigenvectors of the wave function are obtained by the PR wave fluctuation equation, which happens to consist of the natural frequency and its multiples [26–28]. In other words, the arterial pressure wave can be decomposed into individual harmonics in the condition of resonance between the heart and the aorta. Since the fluctuation function of each harmonic frequency is a set of standard orthonormal substrates, this set of harmonic substrates can completely describe the state of the whole system. Therefore, as long as we transform the arterial pressure waves by Fourier transform, we can obtain the amplitude (C_n) and phase (P_n) of each harmonic frequency as a quantitative description of the state of the heart and arterial system [29–31]. Theoretically, the arterial pressure wave can be decomposed into infinite number of harmonics through Fourier transformation, however, clinically we found that the energy of the zeroth to the 11th harmonics accounts for 98% of the total energy of the human arterial pressure wave, so as long as the amplitude and phase of these 12 harmonics are obtained, it is already possible to describe the system state quite accurately and completely. The amplitude C_n and phase P_n of the representative harmonic frequencies after normalization are calculated as follows:

$$f_m(x) = \frac{A_{0,m}}{2} + \sum_{x=1}^{L} A_{n,m} \cos\left(\frac{2\pi n x}{L} - \theta_{n,m}\right)$$

$$C_n = \frac{1}{M}\sum_{m=1}^{M}\frac{A_{n,m}}{A_{0,m}}$$

$$P_n = \frac{1}{M}\sum_{m=1}^{M}\theta_{n,m}$$

where $A(n, m)$ and $\theta(n, m)$ are the amplitude and phase of the nth Fourier series of the mth radial pulse wave measured at one pressure. $A(0, m)$ is the average of the mth radial pulse wave. $f_m(x)$ is the xth data point in the mth radial pulse wave. L is the total number of data points in $P_m(x)$. [32]

In conclusion, under the PR wave motion theory system, most of the work done by the heart on the arterial system is transmitted in the form of elastic potential energy, reducing the energy loss caused by the damping effect between blood and blood vessel walls. Aorta and each organ or vascular cluster synthesize a system with a specific frequency response, its resonance frequency is a whole number of times the heartbeat, so it can effectively and the heart to achieve resonance, greatly enhancing the efficiency of transmission [22,27,30]. Therefore, the heart can drive the blood circulation of the whole body with only a few watts of power. Since the main energy of the arterial pressure waves resonating in the human body is distributed in the first twelve harmonic frequencies, the changes of the human blood circulation can be defined and classified by these twelve variables from a systemic point of view.

3. THE ASSOCIATION OF HARMONIC INDEXES WITH TCM THEORY IN THE VALIDATION OF ANIMAL EXPERIMENTS AND THE APPLICATIONS IN CLINICAL PRACTICE

3.1. Organ Frequency Characteristics and Selective Vasoconstriction of the Vascular Bed

Since 1989, studies in rats have found [21,33–35] that ligation of the renal artery significantly reduces the second harmonic component of the blood pressure wave in the caudal artery; ligation of the splenic artery significantly reduces the third harmonic component. Harmonic analysis of arterial pressure waves suggests that individual organs may have their own specific frequencies. The results of Young et al. [34] further suggest that the effects of ligating organs are linearly iterative. Hsu et al. further demonstrated [35] that the regional selectivity of vasoconstrictor effects on different vascular beds can be assessed using the response of ligated rat organs to arterial blood pressure wave harmonics. Organ artery ligation directly causes a substantial increase in resistance of the organ. Vasoconstrictor drugs can be considered as a gentle ligation procedure, while different doses of drugs can modulate the changes in arterial resistance. In the report, the regional selectivity of vasoconstrictor II and vasopressin, the different ratios of individual effects on arterial pressure harmonics by simple mathematical iterations and the individual effects of ligating the renal artery and the superior mesenteric artery on arterial pressure harmonics are consistent. These results confirm that pressure wave harmonic analysis can determine which arterial bed has increased resistance. Individual vascular beds produce unique, frequency-specific, linearly additive blood pressure wave effects. Thus, simple mathematical calculations can be used to determine the pressure spectrum contribution of each organ. These properties mean that simple analysis of peripheral arterial pressure wave harmonics can be used to diagnose visceral conditions.

The animal experiments and clinical studies described in this subsection show that the 12 harmonics are highly correlated with the 12 meridians described in Chinese medicine. Disturbances in the meridians corresponding to the organs are also fully reflected in the amplitude of the twelve harmonics of the arterial pressure wave. Therefore, we deduce that the twelve harmonic frequencies of the arterial pressure wave can be used to quantify the health status of the organs and the meridians. At present, the correspondence can be inferred and confirmed as follows: C0 – pericardial meridian, C1 – liver meridian, C2 – kidney meridian, C3 – spleen meridian, C4 – lung meridian, C5 – stomach meridian, C6 – biliary meridian, C7 – bladder meridian, C8 – large intestine meridian, C9 – sanjiao meridian, C10 – small intestine meridian [36].

3.2. Effects of Chinese Medicine, Acupuncture, Qigong and Mechanical External Forces on Arterial Harmonics

Studies on herbal medicines in humans and animals have shown that many herbs induce responses in specific frequencies of the arterial blood pressure spectrum, and the classification of herbs by their ascribed meridians is frequency related [37–41]. Systematic studies of Chinese herbal medicines for the Kidney and Spleen meridians [39,40] have also shown that they each have a unique pulse harmonic composition. Studies of herbal formulations [42] further demonstrated that the effect of formulated herbs on the pulse spectrum is a linear iteration of the harmonic effect of single herbs. The effect of feeding the complete Xiao-Jian-Zhong-Tang formulation on the pulse wave spectrum components of blood pressure in rats is similar to the linear composition of the pulse wave spectrum effect of feeding the single drug separately. This linear iterative effect makes it easier to understand and formulate a Chinese herbal formula. We used pulse harmonic analysis to compare two Chinese herbal formulas, Ba-Wei-Dihuang and Liu-Wei-Dihuang, which differed only by two additional mono-drugs and had the same basic composition. This experiment clearly illustrates the logic of pulse harmonic analysis in clinical validation of Chinese medicine [39,41]. These results suggest that blood pressure pulse harmonic analysis can provide a systematic approach to understanding the effects of herbal medicines in Chinese medicine. In addition, in an experiment with black tea and warm water, the changes in radial arterial blood pressure harmonics over time were observed after consumption. The absorption of black tea caused the peripheral small arteries to dilate, and the effect on the arterial system gradually disappeared after 2 hours of drinking black tea. This phenomenon can be described quantitatively by the harmonic characteristics [43]. A comparative study of the effects of green tea and black tea on the circulatory system was also conducted on tea trees from the same farm. We demonstrated that green tea and black tea have different degrees of effects on the arterial system, which can be reflected in quantitative features such as blood pressure and radial arterial pressure wave harmonics. This study illustrates the importance of herbal concoctions that alter the effects of plants on the circulatory system and the effect of food on altering meridians that can be seen by pulse diagnostics [44]. In addition to herbs, harmonic analysis can also be used for general drugs to understand the effects of drug effects on blood distribution [36,45]. Therefore, harmonic analysis has great potential in the early stages of developing new drugs.

Acupuncture points are composed of arterial and small arterial clusters, and acupuncture has the potential to alter the pulse spectrum throughout the body [46–48]. Acupuncture at the Tai-Tsih (K-3), Tsu-San-Li (St-36), and Hsien-Ku (St-43) points induced different changes in blood pressure pulse harmonics, whereas non-acupuncture points did not respond to specific harmonics. Further, we found that acupuncture induced similar spectrum responses to those corresponding to herbs used in Chinese medicine, such as Tsu-San-Li [46] for the spleen meridian [40] and Tai-Tsih [47] for the stomach meridian. This shows that Chinese medicines can be classified and attributed to the meridians according to the characteristics of the harmonics. In addition, the harmonic component can also be used to evaluate the therapeutic effect after acupuncture [49], and the radial pulse was measured before and after the acupuncture treatment in patients with brain injury for harmonic analysis. The results showed a significant increase in C7–C10, representing a change in head circulation after acupuncture. This study also confirmed the correspondence between the harmonic components and meridians.

The feeling of getting qi can be achieved by taking qi tonics (e.g., Ganoderma lucidum) [50], acupuncture [46], or qigong exercises [51], and a similar set of pulse spectrum changes will be obtained in the spectrum analysis – the third, sixth, and ninth harmonics changes, which means that this is a common set of physiological indicators to reflect the changes of the cardiovascular system caused by getting qi. The consumption of coffee and tea [52] also results in similar pulse wave signs, which suggests that getting qi and coffee and tea should affect the same physiological parameters mentioned above.

When we apply a mechanical external force to the arterial system synchronized with the heart or doubled in frequency, the variability of the heart and the variability of the blood pressure pulse harmonic frequency are reduced [53,54]. On the other hand, the second harmonics of the blood pressure pulse decreased when stimulated with 1.5 times the heart rate [54]. These phenomena support our resonance model describing the arterial system in terms of blood pressure transmission and demonstrate the phenomenon of frequency matching. Hsiu et al. further showed [55] that heart rate and blood pressure showed a tendency to change in the same way when stimulated by an external force close to the heart rate or when propranolol was injected into the rat. This suggests that different types of stimuli can induce stabilization mechanisms in the cardiovascular system, observing how the cardiovascular system readjusts to frequency-matched conditions to maintain the transmission efficiency of the arterial system.

3.3. Clinical Monitoring and Disease Prediction

In an animal study of acute liver injury induced by acetaminophen [56], serum glutamate pyruvate transaminase (SGOT) and serum glutamic oxaloacetic transaminase (SGPT), two blood indicators of liver impairment, were found to be highly correlated with the first harmonic amplitude of the blood pressure pulse spectrum. This suggests that blood pressure pulse spectrum analysis may serve as a useful and timely biomarker to complement the monitoring of acute liver injury with SGOT and SGPT. This indicator provides a feasible development of a simple, non-invasive, real-time liver function monitoring device. In clinical studies, blood pressure pulse harmonic analyzers identify correlations with corresponding diseases by analyzing spectral characteristics. In acute myocardial infarction, the second and third harmonics fall first and then increase as the condition improves, with C0 decreasing [57]. Patients with liver problems and workers in chemical plants show abnormal first harmonics [58,59], which is consistent with previous experiments on the association between acetaminophen (Prilosec) and the liver [56].

In a long-term observational study conducted in the domain of metabolism [60–66], we found that the first harmonic frequency (C1) of the radial pulse wave could be an independent predictor of severe cardiac adverse events in 1968 patients with type 2 diabetes without cardiovascular symptoms after a mean follow-up of 1.8 ± 0.4 years through the development of a Cox model and statistical validation of survival analysis in this clinical study [62,63]. A further study identified another independent risk indicator, the fourth harmonic of the radial pulse (C4), which was shown to be associated with the atherosclerotic process and myocardial ischemia. Follow-up results showed an independent negative correlation between C4 values and adverse cardiac events (the lower the C4, the higher the risk of adverse cardiac events) [64]. In addition, C4 variability was also independently and positively associated with diabetic complications [65]. For diabetic retinopathy, harmonic analysis may also provide an assessment of risk [67]. This series of studies has shown that radial pulse waves can profoundly reflect changes in the status of the cardiovascular system. In female physiological studies, it was found that C3 and C5 decreased and C2 and C4 increased in pregnant women. After menopause, C1 increases and C4 decreases in women. This suggests that C4 can be an important cardiovascular risk indicator for women during pregnancy and menopause [68]. In addition, for women of the same age group, C1, C2, and C3 were associated with diabetes risk after excluding the effects of age and blood pressure, especially in C3, which was found to be a predictor of diabetes risk by ROC curve analysis [69].

The variability of the pulse spectrum has been applied to the study of terminally ill patients and overanesthetized rats on the verge of death. There is no significant change in diastolic and systolic blood pressure during the process of dying, however, the harmonics of blood pressure pulses gradually lose their stability from the higher frequencies and then the lower frequencies as well. This suggests that the variability of pulse harmonics may be correlated with health status and may be a predictor of a life's approach to death [70,71].

3.4. The Effect of Daily Activity on the Pulse

Daily human activity may induce effects on the frequency spectrum of blood pressure pulses on specific harmonics, because different activities may require different amounts of blood in different parts of the body. It was found [72] that the ratio of the second harmonic (C2) to the fourth harmonic (C4) of the blood pressure pulse will increase significantly after eating. The steady state is reached after about half an hour of food intake, and this state is maintained for about 3 to 4 hours. This means that during this period, more blood is delivered to the corresponding parts of the stomach, trachea, bronchi and extremities. In addition, in another study, we also observed systematic changes in the blood pressure pulse spectrum when subjects were lying down and relaxed [73], and their relatively weak harmonic components were enhanced. Although the composition of the detailed spectral changes varies between subjects, the changes are consistently repeated for the same subject. This suggests that rest is effective in the healing of disease.

4. USING PHOTOPLETHYSMOGRAPHY FOR PREDICTING DISEASE RISK BY HARMONIC INDEXES

In the study by Dr. Liao and Dr. Wang [67], besides finding that the harmonic index could predict diabetic retinopathy, the photoplethysmography (PPG) signal was also shown to be as useful as the radial arterial pulse signal. We extended the above study and further used PPG signals with harmonic indices in the same study (ISRCTN14306167) for more different disease prediction applications.

Diabetes mellitus can be classified as a syndrome of Xiao Ke in the clinical diagnosis and treatment of Chinese medicine. With the disease progressing with the occurrence of complications, it can be seen as liver and kidney yin-deficiency or yin-yang two-deficiency [74]. The PPG signal is similar to the radial arterial pressure signal, which is derived from the interaction of heartbeat and arterial pulsation. Many studies have demonstrated that the two are highly correlated and can respond to the same physiological changes or be used in the assessment of disease risk [67,75]. In a study of 2408 diabetic patients after excluding those who had complications at the time of enrollment with an average 3.75 ± 1.62 years of follow-up, the association of PPG signals with different diabetic complications was observed using harmonic analysis to obtain the proportion of each harmonic of the pulse representing different meridians. (ISRCTN14306167) The distribution of the proportion of harmonics affected by different comorbidities was statistically significant ($P < 0.05$) compared to patients without any comorbidity for an average of 3.75 years. Among them, peripheral arterial occlusion disease (PAOD) was associated with C3, C4, C5, C6 and C9; diabetic peripheral neuropathy (DPN) was associated with C0, C1 and C8; diabetic retinopathy (DR) was associated with C0, C1, C3, C4, C7 and C9; major adverse cardiovascular events (MACE, including stroke, myocardial infarction and cardiac death) were associated with C3; and major adverse renal events (MARE, including 2-fold increase in blood creatine, end-stage renal disease and renal death) were associated with C0, C1, C4 and C7. The results are consistent with previous studies in radial arterial pulses [76] and suggest that the pulse harmonic proportion may provide a possible mechanism for the hemodynamics of diabetic complications in TCM, and may also be used as a predictor of various complications of diabetes (Table 1).

In another heart disease study, 76 patients (47 men and 29 women) were enrolled in the Beijing university of chinese medicine third affiliated hospital, including 62 patients with coronary artery disease and 14 patients with heart failure, with an average age of 66.6 years. Compared to healthy 20-year-olds, patients with coronary artery disease and heart failure had common characteristics of low C0 and C3 and high C1 and C2. This phenomenon represents poor circulation in the cardiac and digestive systems. In the presence of poor cardiac output, the liver circulation increases to metabolize the waste products produced by systemic hypoxia. Further, Logistic regression analysis was used to differentiate patients with coronary artery disease from those with heart failure, and C0 (OR = 2.864, CI = 1.438–7.96, $P = 0.01$) and C3 (OR = 6.713, CI = 2.363–3.414, $P = 0.009$) remained as independent influences after correction for age, body mass index, and heart rate. The ROC curve (Figure 1) was generated by using the harmonic indexes C0, C3 and age to predict heart failure, and the area under the curve (AUC) was 0.871.

Table 1 | Comparison of physiological parameters, harmonics (C_n) and non-complications for different complications (mean ± standard deviation)

	Without complication	PAOD	DPN	DR	MACE	MARE
Number (*n*)	1215	73	430	322	303	123
Male (%)	48.6	37.5	59.6	55.0	59.8	54.5
Age (year)	60.1 ± 10	63.9 ± 13.9*	66 ± 12.8*	65.6 ± 12.5*	66 ± 12.6*	68.5 ± 13.2*
BMI (kg/m^2)	26.2 ± 4.4	27.6 ± 4.5*	26.5 ± 4.5	26.4 ± 4.5	26.9 ± 4.7*	27.1 ± 3.9*
Waist circumference (cm)	94.8 ± 65.6	94.8 ± 12	93.1 ± 11.1	96.4 ± 63	105.8 ± 107.4	96.2 ± 10.3
SBP (mmHg)	126.6 ± 11.1	126.9 ± 11.5	128.9 ± 12.6*	129.9 ± 13*	127.4 ± 10.2	131.7 ± 15.5*
DBP (mmHg)	74.6 ± 7.8	73.3 ± 7.9	75.8 ± 32.1	74.4 ± 8	76.8 ± 38.1	73.4 ± 8.4
Heart rate (beat/second)	71.6 ± 11.6	78.1 ± 11.8*	72.6 ± 12.5	73.8 ± 12.7*	72.7 ± 12.6	74.2 ± 14.7*
HbA1C (%)	7.1 ± 1.4	7.4 ± 1.5	7.2 ± 1.5	7.3 ± 1.3*	7.3 ± 1.5	7.5 ± 1.6*
ACR (mg/g)	9.4 ± 10.8	117.3 ± 328*	244.5 ± 742.8*	282.9 ± 869.8*	271.8 ± 717.5*	1112.7 ± 1621*
eGFR (mL/min/1.73 m^3)	97.6 ± 26	81.5 ± 41.9*	82.8 ± 33.4*	82.5 ± 35*	79.8 ± 35.7*	48.1 ± 39.7*
Hypertension (%)	40.2	68.5	66.2	64.6	67.3	75.9
Hyperlipidemia (%)	64.4	74.0	65.8	69.3	69.6	69.6
Smoke (%)	16.9	16.4	18.4	14.0	21.0	17.9
C0	0.515 ± 0.071	0.514 ± 0.062	0.508 ± 0.072*	0.506 ± 0.068*	0.514 ± 0.067	0.487 ± 0.077*
C1	1.619 ± 0.617	1.585 ± 0.443	1.683 ± 0.675*	1.687 ± 0.565*	1.593 ± 0.525	1.756 ± 0.594*
C2	0.415 ± 0.287	0.424 ± 0.087	0.409 ± 0.098	0.404 ± 0.13	0.408 ± 0.193	0.421 ± 0.171
C3	0.459 ± 0.102	0.421 ± 0.09*	0.452 ± 0.105	0.429 ± 0.114*	0.445 ± 0.106*	0.439 ± 0.121
C4	0.544 ± 0.345	0.606 ± 0.227*	0.535 ± 0.217	0.592 ± 0.251*	0.549 ± 0.246	0.603 ± 0.287*
C5	0.821 ± 0.216	0.757 ± 0.192*	0.81 ± 0.24	0.801 ± 0.237	0.825 ± 0.249	0.799 ± 0.289
C6	0.675 ± 0.257	0.604 ± 0.132*	0.678 ± 0.209	0.655 ± 0.22	0.683 ± 0.209	0.683 ± 0.23
C7	0.617 ± 0.171	0.641 ± 0.131	0.627 ± 0.168	0.646 ± 0.179*	0.619 ± 0.181	0.676 ± 0.204*
C8	0.733 ± 0.229	0.706 ± 0.142	0.702 ± 0.182*	0.734 ± 0.213	0.733 ± 0.199	0.712 ± 0.176
C9	0.76 ± 0.201	0.695 ± 0.118*	0.75 ± 0.219	0.728 ± 0.19*	0.782 ± 0.323	0.764 ± 0.376

BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; ACR, Albumin to creatinine ratio; eGFR, estimated glomerular filtration rate; LDL, Low-density lipoprotein cholesterol; HDL, High-density lipoprotein cholesterol; C_n, the *n*th harmonic component; PAOD, Peripheral arterial occlusion disease; DPN, Diabetic peripheral neuropathy; DR, Diabetic retinopathy; MACE, Major adverse cardiovascular events; MARE, Major adverse renal events.

*Asterisks indicate that the means of variables in with complications group differ significantly from without complications group. ($P < 0.05$)

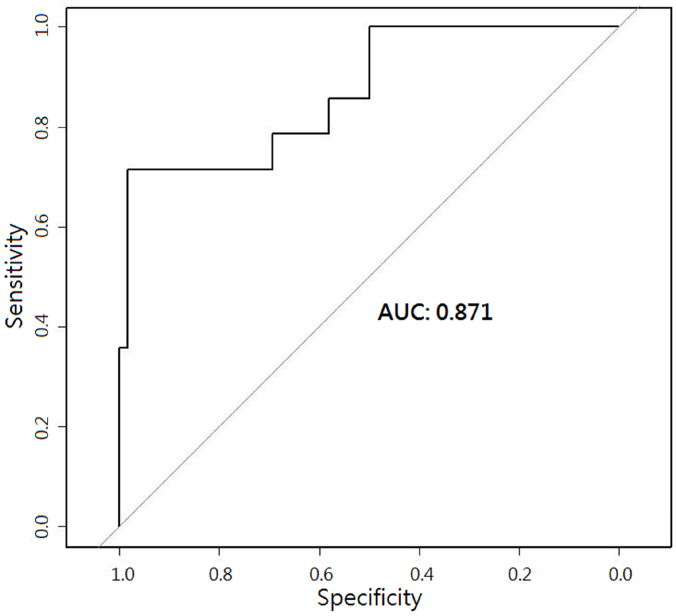

Figure 1 | ROC curves for the harmonic indexes of photoplethysmography signals to predict heart failure.

The results are consistent with previous studies in radial arterial pulses [60,66]. This study demonstrates that the harmonic indexes of PPG signals can be used to predict the occurrence of heart failure in patients with heart disease, and also illustrates the hemodynamic impact of coronary heart disease and heart failure.

5. CONCLUSION

The purpose of this study is to propose a feasible approach for the modernization of TCM. Meridian theory has provided a systematic description of TCM for thousands of years, but is very different from the modern Western medical description of physiology. In this study, a radial resonance theory model is developed from a biophysical perspective. Various physical, prosthetic, and animal experiments are used to verify the physiological functions of the various harmonics corresponding to the TCM meridians represented in the model. The physiological mechanism of TCM theory is explained in a scientific way, and a bridge between TCM and modern Western medicine is established. It also demonstrates the practical application of radial resonance theory in clinical monitoring.

In the East, pulse diagnosis has been a unique method of diagnosis in TCM for thousands of years. In the West, two thousand years ago, the Greek physician Galen emphasized the importance of feeling the pulse for health and described in detail the pulse changes due to age, sex, season, exercise, sleep, pregnancy, bathing, food, and wine [77]. Harmonic analysis of the arterial pulse has been used by researchers to study the frequency characteristics of organs; to explore the meridian theory of TCM; and to find the effects of herbs [37–42], coffee, tea [43,44], acupuncture [45–47], fasting [78], and exercise [79]. In clinical monitoring, it has also been used to associate harmonic spectra with some cardiovascular risk factors [60–66], and female physiological states [68]. With the advances in sensing technology, there are more and more portable and accurate tools for measuring arterial signals, such as the PPG products. The quantitative analysis of arterial pulses applied to an individual's daily activities can validate their effectiveness for individuals seeking a healthy life. This technique has great potential to be used as a non-invasive method for decision support in health protection and quality of life protection. It can also help to explore the principles of the cardiovascular system's response to redistribute its power or blood in the face of different life situations. Therefore, we conclude that the development of quantitative pulse diagnostics using radial hemodynamic theory could pave the way for the future of personalized health care.

STATEMENTS AND DECLARATIONS

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contribution

GCW, SHW contributed in conceptualization, methodology, investigation, formal analysis and writing the original draft. KML, CB, YY, HL contributed in conceptualization, resources, data curation and writing – review. TCW and YYLW were involved in conceptualization, methodology, validation and writing – review & editing the manuscript.

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Data Availability Statement

The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Abbreviations

TCM:	traditional Chinese medicine
PR wave:	radial pressure wave
SGOT:	serum glutamate pyruvate transaminase
SGPT:	serum glutamic oxaloacetic transaminase
C_n:	the *n*th harmonic component, $n = 0–10$
P_n:	the *n*th harmonic phase, $n = 1–10$
PPG:	photoplethysmography
BMI:	Body mass index
SBP:	Systolic blood pressure
DBP:	Diastolic blood pressure
ACR:	Albumin to Creatinine ratio
eGFR:	estimated glomerular filtration rate
LDL:	low-density lipoprotein cholesterol
HDL:	high-density lipoprotein cholesterol
PAOD:	peripheral arterial occlusion disease
DPN:	diabetic peripheral neuropathy
DR:	diabetic retinopathy
MACE:	major adverse cardiovascular events

MARE: major adverse renal events
OR: odds ratio
CI: confidence interval
ROC curves: receiver operating characteristic curve
AUC: area under the curve

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