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Application of Phase Analysis Technology in CZT-SPECT Myocardial Perfusion Imaging in the Field of Cardiovascular Diseases

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Abstract

The advent of cadmium-zinc-telluride semiconductor single-photon emission computed tomography (CZT-SPECT) marks a major technological breakthrough in the field of nuclear cardiology. Based on traditional imaging of myocardial perfusion (MPI), the derived phase assessment technology has realized a leap from static blood flow assessment to dynamic evaluation of myocardial mechanical contraction synchrony. As a core analytical technology of gated myocardial perfusion imaging (GMPI), phase analysis generates phase maps, amplitude maps, phase cine loops, and phase histograms through reconstruction to quantitatively assess left ventricular mechanical contraction synchrony. With the continuous advancement of CZT-SPECT, acquisition protocols, image reconstruction algorithms, and artificial intelligence technologies, the application scope of phase analysis in the precision diagnosis and treatment of cardiovascular diseases continues to expand. This article systematically reviews the technical principles of CZT-SPECT phase analysis, its clinical applications in various cardiovascular diseases, the current challenges, and future development directions, intending to serve as a thorough reference for clinical application and academic research.

Keywords

CZT-SPECT, Myocardial Perfusion Imaging, Phase Analysis, Mechanical Synchrony, Cardiovascular Conditions

1. Introduction

Cardiovascular diseases are one of the leading causes of death worldwide, and they

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rank first among the causes of death for urban and rural residents in China, with 2 out of every 5 deaths attributed to cardiovascular diseases [1]. Therefore, early identification of cardiac function impairment is crucial for improving patient prognosis. Having undergone decades of development, gated nuclear myocardial perfusion imaging (GMPI) has become a cornerstone non-invasive imaging technology for diagnosing coronary artery disease, evaluating myocardial viability, and predicting prognosis [2]-[4]. The clinical application of conventional single-photon SPECT is primarily to identify abnormalities in myocardial blood flow distribution, with little to no involvement in the assessment of cardiac systolic synchrony. The essential function of the heart lies in its precise electromechanical coupling and coordinated, orderly contraction. Left ventricular mechanical dyssynchrony plays a key pathophysiological role in the development and progression of heart failure and is closely associated with patients' clinical symptoms, health-related quality of life, and long-term clinical prognosis [5]-[7]. For a long time, the assessment of cardiac mechanical function, especially the quantification of synchrony, has mainly relied on echocardiographic techniques such as tissue Doppler imaging and speckle tracking imaging [8]. The limitations of conventional SPECT have been overcome by the advent of the CZT-SPECT system. CZT-SPECT technology is not a simple improvement over traditional sodium iodide crystal SPECT, but rather a radical change from detection principle to system architecture [9]. CZT-SPECT possesses excellent photon detection sensitivity, energy resolution, and fast acquisition capability [10]. These advantages not only elevate the image quality, diagnostic accuracy, and patient experience of MPI to unprecedented heights but also facilitate the emergence of an advanced post-processing technique—namely, phase analysis technology derived from conventional gated myocardial perfusion imaging data [11]. The emergence of phase analysis technology enables us to understand not only myocardial blood flow perfusion but also myocardial contraction synchrony, thus realizing a comprehensive assessment of cardiac function. This article systematically reviews the clinical application evidence and significance of phase analysis technology in cardiovascular diseases, including heart failure, coronary artery disease, and cardiomyopathies, and discusses its future development directions, aiming to provide multi-perspective references for clinical practice and scientific research.

2. Basic Principles of Phase Analysis in CZT-SPECT

During gated myocardial perfusion imaging (MPI) acquisition by CZT-SPECT, the patient's electrocardiogram is recorded synchronously, and each R-R cardiac cycle is evenly divided into 8 or 16 time bins (phases) in general. After reconstruction, a series of three-dimensional (3D) image datasets is obtained, representing the instantaneous morphology and count distribution of the heart at different time points during systole and diastole. During systole, the thickening amplitude of the local ventricular wall is highly correlated with local myocardial blood flow. In gated MPI, the change in radioactive counts in a specific myocardial region during the cardiac cycle can effectively reflect the thickening and thinning process of the ventricular wall in that region. Through 3D reconstruction and analysis of images of these time bins, the algorithm automatically tracks the count-time curve of radioactive counts in each myocardial segment. Using Fourier transform or other mathematical methods, the count-time curve of each segment is converted into its "phase", *i.e.*, the time point when the segment starts to contract, usually expressed as an angle (0˚ - 360˚) relative to the entire cardiac cycle [12].

Parameter Generation and Visualization:

1) Phase Map

The calculated phase angles (ranging from 0˚ to 360˚, corresponding to the entire cardiac cycle) are projected onto a 3D ventricular model or a polar bull's-eye map in a color-coded manner to form an intuitive "systolic timing map".

2) Phase Histogram

The distribution frequency of phase angles of all myocardial segments is counted to generate a histogram, from which two most critical quantitative parameters are derived [13]: Standard Deviation of Phase (PSD), the phase angle standard deviation for all segments, reflecting the overall systolic dispersion; Phase Histogram Bandwidth (PHB), the range of phase angles containing 95% of segments on the histogram, reflecting the time difference between the earliest and latest contracting segments.

3) Phase Cine Loop

Dynamic playback of the 3D cardiac model with colors indicating the sequence of contraction, providing an intuitive visual assessment of the excitation conduction pathway.

In the same examination on the same device, phase parameters can be obtained and analyzed simultaneously alongside perfusion defect extent, the left ventricle's ejection fraction (LVEF), ventricular thickening rate, and other parameters, achieving a true 3D whole-heart assessment with high cost performance. The phase analysis process is highly automated, reducing operator dependence, and the measurement results have good reproducibility, which facilitates long-term follow-up and efficacy assessment.

3. Application of CZT-SPECT Phase Analysis in Patients with Heart Failure

Heart failure is a manifestation of various cardiovascular diseases that have progressed to an advanced stage or terminal phase. A Chinese heart failure epidemiological survey conducted between 2012 and 2015 reported a prevalence of 1.3% in the population aged ≥ 35 years, up 0.4% from the year 2000 [14]. Heart failure is caused by abnormal changes in cardiac structure and function due to various etiologies, leading to varying degrees of left ventricular systolic and diastolic dysfunction, which in turn induces left ventricular mechanical dyssynchrony. There are significant differences in mechanical dyssynchrony patterns caused by different etiologies, and CZT-SPECT-based phase analysis of myocardial perfusion imaging provides a unique differential perspective for this.

3.1. Identification and Risk Stratification of Different Heart Failure Subtypes

Dyssynchrony is common in patients with heart failure, but there are significant differences in mechanical dyssynchrony patterns caused by different etiologies. CZT-SPECT phase analysis provides a unique differential diagnostic perspective in this regard.

Phase analysis of heart failure caused by ischemic cardiomyopathy (ICM) usually shows segmental mechanical contraction delay consistent with the coronary blood supply area, while that of heart failure caused by non-ischemic/dilated cardiomyopathy (NICM/DCM) shows more diffuse patterns, often manifested as multi-regional, non-segmental mechanical contraction delay [15]. Li Duoduo *et al.* [16] obtained GMPI phase analysis parameters from 80 healthy subjects: PHB (39.8 ± 14.4)˚, PSD (13.7 ± 7.4)˚. The occurrence of phase delay in the lesion area will lead to an increase in PHB and PSD, indicating a higher degree of left ventricular mechanical contraction dyssynchrony [17]. The phase analysis parameters proposed by Henneman MM *et al.* [18] (such as PSD > 43˚ and PHB > 135˚) have been validated by multiple studies as independent predictors of major adverse cardiovascular events in patients with heart failure. This indicates that CZT-SPECT phase analysis provides a new tool for precise risk stratification in heart failure.

3.2. Identification of Appropriate Candidates for Cardiac Resynchronization Therapy and Prediction of Treatment Response

When patients develop drug-refractory heart failure accompanied by cardiac dyssynchrony, the adoption of cardiac resynchronization therapy (CRT) is an important treatment strategy. However, the traditional use of electrocardiographic QRS wave width (usually > 120 - 130 ms) as the standard for dyssynchrony and the main basis for patient selection results in approximately 30% of implant recipients having no therapeutic response [19]. Multiple prospective studies have confirmed [20] that mechanical dyssynchrony indicators provided by phase analysis are powerful tools for predicting CRT efficacy, with PSD regarded as the core indicator.

Henneman *et al.* [18] suggested that baseline PSD > 43˚ can significantly distinguish CRT responders from non-responders, and its predictive accuracy (AUC 0.7 - 0.8) is stably superior to QRS wave width. For patients in the “gray zone” with QRS wave width between 120 and 150 ms and those with right bundle branch block, the differential value of phase analysis is particularly prominent, which can make up for the limitations of QRS wave width; therefore, phase analysis can be used for preoperative screening.

The efficacy of CRT depends not only on the presence of dyssynchrony, but also on whether the left ventricular pacing electrode can be placed at the phase of the latest mechanical contraction [21]. Phase cine loops can intuitively and three-dimensionally display this "latest activated region (LAR)", and phase maps can provide clinicians with the region of the latest systolic phase to guide the selection of appropriate targets for pacing lead implantation during surgery [22]. Boogers MJ *et al.* [23] showed that when the pacing electrode position was consistent with the LAR determined by phase analysis, The proportion of patients with a >15% improvement in left ventricular ejection fraction was significantly increased, and left ventricular end-diastolic volume and end-systolic volume were significantly improved; in contrast, no significant changes were observed in these indicators when the pacing electrode position was inconsistent with the LAR determined by phase analysis. Therefore, localization of the latest activated region by phase analysis can guide individualized implantation. Zou Jiangang *et al.* [24] enrolled 180 patients and randomly assigned them to a control group and a guidance group. Preliminary results showed that, in CRT treatment, the group of patients receiving phase analysis-guided left ventricular lead implantation had better efficacy than the traditional implantation group. This confirms that phase analysis technology can guide the site of left ventricular lead implantation, and that selecting the latest contracting segment as the left ventricular lead implantation site while avoiding infarcted areas can significantly improve the efficacy of CRT.

Postoperative follow-up phase analysis of CRT can evaluate the therapeutic effect of CRT by comparing the improvement of parameters such as PSD and PHB. Studies have shown [25] [26] that significant improvement in synchrony after surgery is closely associated with hard endpoints such as LVEF elevation, left ventricular reverse remodeling, reduced heart failure hospitalization rate, and improved long-term survival rate. In addition, it can be used to optimize pacemaker parameter settings (e.g., atrioventricular delay, interventricular delay), and the personalized scheme for achieving the best mechanical synchrony can be found by comparing phase parameters under different programming settings. An international multi-center study including 19,210 patients showed [27] that three phase parameters (PSD, PHB, and phase entropy) were significantly associated with adverse cardiac events, which increased with the elevation of phase parameters. The cut-off values of cardiac adverse events predicted by software were entropy 39.5%, PHB 42˚, and PSD 7.9˚. Differences in software platforms, study populations, and endpoint definitions render these cut-off values non-interchangeable across studies.

4. Application of CZT-SPECT Phase Analysis in Coronary Artery Disease

4.1. Assessment of Myocardial Ischemia and Myocardial Viability

Coronary artery stenosis leads to reduced myocardial blood flow perfusion, which in turn triggers myocardial ischemia or myocardial infarction, accompanied by altered cardiac systolic synchrony. Phase analysis, which quantifies this systolic synchrony, provides an indirect indicator for assessing the severity of coronary artery disease (CAD). A study by Van Tosh *et al.* [28] demonstrated that stress-induced myocardial ischemia can trigger regional systolic timing delay, manifested as significantly elevated phase standard deviation (PSD) and phase histogram bandwidth (PHB) under stress compared with rest. The stress-rest phase difference can identify ischemia-related mechanical dyssynchrony, and its sensitivity outperforms that of pure perfusion imaging—especially in patients with three-vessel coronary ischemia or microvascular disease—with an approximately 15% - 25% improvement in sensitivity over perfusion imaging alone.

When myocardial ischemia is induced by stress tests (exercise or pharmacologic), the ischemic myocardial segments not only present with reduced blood flow perfusion, but also exhibit changes in systolic function, manifested as phase delay. By comparing the changes in phase parameters between stress and rest conditions, we can identify stress-induced cardiac mechanical dyssynchrony, which provides a technical basis for comprehensive and accurate assessment of cardiac function and myocardial ischemia.

Combining myocardial perfusion imaging with PET glucose metabolic imaging enables the assessment of myocardial viability. Studies have shown [18] that by fusing phase maps with myocardial perfusion images, we can clearly distinguish three types of myocardial tissue: 1) Normal myocardium, characterized by normal perfusion and normal phase; 2) Viable myocardium or non-transmural infarction, which presents with reduced perfusion but normal phase; 3) Inactivated infarcted tissue, indicated by reduced perfusion accompanied by phase delay. This comprehensive analysis enhances the ability to discriminate the state of myocardial tissue. Zhang *et al.* [29] performed technetium-99m methoxyisobutylisonitrile myocardial perfusion imaging and fluorine-18 fluorodeoxyglucose myocardial metabolic imaging in 91 patients with a documented history of myocardial infarction, combining both to assess myocardial viability. In patients with myocardial infarction, the amounts of hibernating myocardium and infarcted myocardium were significantly higher in those with left ventricular dyssynchrony (LVMD) than in those without LVMD. Phase bandwidth can reflect the extent of hibernating myocardium and infarcted myocardium; whereas in patients with myocardial infarction, hibernating myocardium is independently associated with LVMD.

4.2. Assessment of Coronary Microcirculatory Function

Coronary microvascular dysfunction represents an important component of coronary artery disease, yet it remains difficult to assess via conventional imaging modalities. CZT-SPECT phase analysis technology provides a new approach for indirectly assessing microcirculatory function. Studies have shown [30] [31] that a diffuse, non-segmental increase in phase parameters (PSD, PHB) after stress without obvious epicardial coronary artery stenosis may indicate the presence of extensive microcirculatory dysfunction. This serves as a valuable indirect marker for clinical diagnosis of cardiac coronary microcirculatory lesions or evaluation of the impact of diseases such as diabetes and hypertension on the microcirculation. The evidence base is limited, and validation through dedicated flow quantification or invasive testing is still warranted.

5. Application of CZT-SPECT Phase Analysis in the Diagnosis and Differential Diagnosis of Special Cardiomyopathies

5.1. Application in Hypertrophic Cardiomyopathy (HCM)

In patients with HCM, extreme hypertrophy and fibrosis of the interventricular septum often impede excitation conduction, resulting in a significant delay in septal contraction, whereas the lateral wall is relatively earlier activated. Chen *et al.* [32] studied 32 patients with hypertrophic cardiomyopathy who underwent resting myocardial perfusion imaging before and after alcohol septal ablation. Through phase analysis, it has been found that patients with hypertrophic cardiomyopathy often exhibit septal contraction delay and left ventricular dyssynchrony, manifested as septal activation occurring later than lateral wall activation. Left ventricular dyssynchrony was significantly improved after alcohol septal ablation. Phase analysis can accurately depict the abnormal myocardial activation sequence and has important clinical value.

5.1.1. Identification of Occult Dyssynchrony

In the setting of normal or even supranormal left ventricular ejection fraction, many patients with hypertrophic cardiomyopathy (HCM) already exhibit significant septal-to-lateral wall systolic dyssynchrony, and phase analysis can quantify this abnormality.

5.1.2. Assessment of Obstruction Risk and Mechanism

Phase cine loops can dynamically display the abnormal excitation and contraction patterns of the interventricular septum, helping to understand the dynamic mechanism of left ventricular outflow tract obstruction.

5.1.3. Prediction of Ventricular Arrhythmia Risk

Severe mechanical dyssynchrony is associated with myocardial electrical activity disorders. Studies have shown [33] that HCM patients with large phase dispersion may face a higher risk of ventricular arrhythmias.

5.2. Application in Dilated Cardiomyopathy (DCM)

In DCM, the patterns of phase dyssynchrony are diverse, which may be diffuse heterogeneous delay, or there may be a definite latest activation of the lateral or posterolateral wall. Wang *et al.* [34] conducted a follow-up study of resting myocardial perfusion imaging in 52 patients. The study showed that deceased patients had more severe left ventricular systolic dyssynchrony; phase entropy served as an independent predictor of heart failure, indicating that phase parameters are of significant value for prognostic assessment in patients with dilated cardiomyopathy. Xu Zhihui *et al.* [35] retrospectively studied 72 patients with dilated cardiomyopathy, and the results demonstrated that phase entropy was an independent predictor of adverse cardiac events.

6. Current Challenges and Future Development Directions

6.1. Challenges and Limitations

Despite its significant advantages, the clinical popularization of CZT-SPECT phase analysis still faces challenges.

6.1.1. Standardization and Establishment of Reference Values

Differences exist in CZT-SPECT devices and post-processing algorithms from different manufacturers, leading to the lack of a unified normal reference range for the absolute values of phase parameters. At present, most centers rely on reference values provided by equipment manufacturers or establish their own reference databases, and large-scale multicenter studies are urgently needed to establish universal standards.

6.1.2. Dependence on Image Quality

In patients with extremely low doses, severe obesity, or cardiac arrhythmias (e.g., atrial fibrillation), low image count rate or irregular cardiac cycles will affect the accuracy of phase analysis.

6.1.3. Depth and Breadth of Clinical Verification

Although it has a good correlation with technologies such as ultrasonic speckle tracking and MRI, the evidence from prospective, large-scale randomized controlled studies on phase analysis parameters guiding specific clinical decisions (e.g., the final decision of CRT implantation) still needs to be further enriched.

6.2. Future Prospects

6.2.1. In-Depth Integration with Artificial Intelligence

The use of deep learning algorithms is expected to automatically identify abnormal phase patterns, predict disease subtypes or prognosis, and further reduce the dependence on operator experience.

6.2.2. Multi-Parameter Fusion Analysis

By integrating phase analysis with the absolute quantification of myocardial blood flow function using CZT-SPECT, a “one-stop” comprehensive assessment platform that incorporates perfusion, blood flow, function, and synchrony can be constructed, providing an unprecedented panoramic view of myocardial pathophysiology.

6.2.3. Expanded Application of New Tracers

Exploring the combination of phase analysis with PET tracers such as ^{18}F-FDG to deepen the understanding of disease mechanisms from the perspective of molecular imaging.

7. Conclusion

The CZT-SPECT phase analysis technique has successfully extended the assessment of the myocardium from the static domain of blood flow distribution to the dynamic domain of cardiac mechanical coordination. Relying on its core advantages of being non-invasive, three-dimensional, objective, reproducible, and homologous with perfusion information, it has become an indispensable tool in the nuclear cardiology toolkit, providing a powerful means for the diagnosis, differentiation, treatment decision-making, and prognostic assessment of heart failure (especially CRT treatment), coronary artery disease, and various special cardiomyopathies.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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