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REVIEW ARTICLE—FOCUS ISSUE: CARDIAC SARCOIDOSIS UPDATE

# Nuclear Medicine Image Interpretation Progress in the Assessment of Cardiac Sarcoidosis: July 2019 ASNC/JSNC Joint Session

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Abstract

**Sarcoidosis is a significant disease affecting the heart. $^{18}$F-fluorodeoxyglucose (FDG) positron emission tomography (PET) is a well-validated method for identifying significant focal inflammatory sarcoid lesions. The recent progress in image interpretation in nuclear medicine improves the diagnosis and the risk stratification in patients with cardiac sarcoidosis. Especially, metabolic activity, texture analysis, phase analysis, right ventricle assessment, and digital PET/CT are promising methods to assess cardiac sarcoidosis. This review focuses on the latest data analyses and image interpretation used in nuclear medicine to assess cardiac sarcoidosis.**
**Keywords: Cardiac sarcoidosis, Metabolic activity, PET, Phase analysis, RV assessment, Texture analysis**
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$^{18}$F-fluorodeoxyglucose (FDG) positron emission tomography (PET) is a valuable imaging modality for the delineation of inflammatory sarcoid lesions including the heart, lung, spleen, muscle, lymph nodes, and other organs. The strengths of nuclear medicine for the evaluation of cardiac sarcoidosis (CS) are its noninvasiveness and low rate of contraindication, its high sensitivity for inflammatory sarcoid lesions with FDG uptake, its excellent diagnostic performance for perfusion defects, and its ability to monitor the effects of steroid therapy. Our recent study and those of others demonstrate that the latest imaging data analysis improves the diagnostic value and risk stratification in patients with CS (1, 2). This review focuses on the latest data analysis and its interpretation used in nuclear medicine to assess CS.

## Data analysis for cardiac sarcoidosis

A 2018 update from the Japanese Society of Nuclear Cardiology demonstrated that the combination of FDG and perfusion PET findings can be classified into three patterns (3) that can be used for the risk stratification of patients with suspected cardiac sarcoidosis (4). The presence of both focal perfusion defect and FDG uptake predicts a poor outcome in patients with known or suspected CS. However, the heterogeneity of spatial abnormality was not taken into consideration in that study (4), although inflammation and scar lesions are heterogeneous in the heart (5). Accordingly, the precise evaluation of the disease heterogeneity should improve the diagnostic and prognostic values.

Many challenges and unresolved issues remain regarding the evaluation of CS. For example, the quantification of the metabolic volume and activity and the estimation of the heterogeneity of disease activity are important tasks to be addressed (6). The assessment of right ventricular (RV) lesions is also useful for the risk stratification of patients with cardiac sarcoidosis (1). Higher spatial and temporal resolution is also desired for the further precise evidence of cardiac involvement.

## Metabolic activity

The maximum standardized uptake value (SUVmax) has been used for semiquantitative measurements in the evaluation of the intensity of FDG uptake. Volume-based analyses (such as analyses of the cardiac metabolic volume [CMV] and cardiac metabolic activity [CMA]) have been used to assess the extent and activity of the FDG uptake in cardiac lesions (7). The CMV is measured by contouring margins defined by some thresholds such as the liver uptake or the blood pool SUV (Figure. 1). The CMA is calculated by multiplying the

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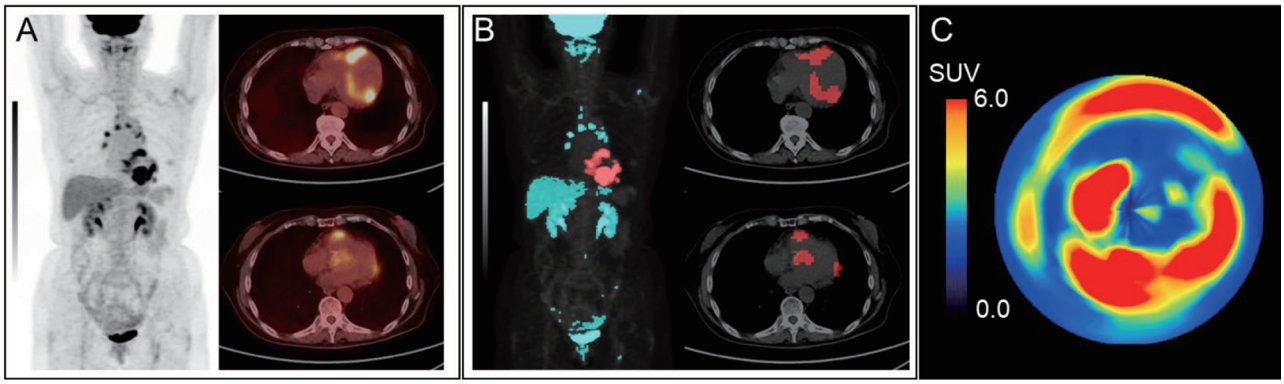


**Figure 1** Quantitative analysis of cardiac uptake.
**A**: A maximum intensity projection (MIP) image of FDG PET and axial images of PET/CT. There are focal uptakes not only on the LV but also on the RV due to the patient's active CS. All of the voxels with an SUV over the defined threshold (on this occasion, 1.5 times the SUVmean in the aortic blood pool) are extracted; red=cardiac lesions, aqua=extra-cardiac lesions (**B**). In this patient's case, the SUVmax, CMV, and CMA were calculated as 10.7, 82.2 ml, and 361.1 ml, respectively. The polar map is created for the evaluation of the FDG distribution and heterogeneity in the LV (**C**).

average of the SUV by the metabolic volume (6). The determination of the quantitative metabolic activity is useful for the quantification of the metabolic volume and activity and for monitoring longitudinal FDG examinations to guide the use of steroid therapy. Ahmadian et al. reported that the CMA was a reliable independent predictor of cardiac events in patients with CS (7).

**Texture analysis**

Recent studies note that the evaluation of FDG heterogeneity in myocardium provides diagnostic and prognostic advantages for CS patients (8, 9). A texture analysis (TA) is comprised of a group of computational methods that extracts information about relationships among adjacent pixels (2D) or voxels (3D) and evaluates the inhomogeneity. The measurement of textural features may allow better tissue characterization for in-depth assessments of PET images than is possible with the current parameters such as the SUVmax. A TA provides informative parameters that can be used to diagnose CS in terms of the quantification of the heterogeneous uptake of FDG, which cannot be captured by a visual assessment in humans. Our recent study included 21 patients with CS and 53 patients with non-CS. Texture features (as described by Orlhac (10)) are measured by using the home-made PTexture package (1). The SUV and CMV are widely overlapped between CS with pathological uptake and non-CS with physiological uptake when only 6-hr fasting is applied (1). However, 16 of the 36 texture features can discriminate CS from non-CS. The long-run emphasis (LRE), a type of gray-level run length matrix, is the best discriminator of CS. The diagnostic value of the LRE is also significantly higher than those of the SUVmax and CMV (1).

In a receiver operating curve (ROC) analysis, the cut-off value of the LRE was 13.3. It is difficult to assess the patterns of polar maps of FDG by a visual method, but the assessment can be achieved by using the LRE, which is also a type of texture feature. These cases clearly show that texture features discriminate CS patients beyond a visual assessment. The inter-operator reproducibility of TA is high, with an intraclass correlation coefficient of 0.98. Another study demonstrated that an FDG texture analysis was useful to evaluate the association between texture parameters for FDG heterogeneity and prognosis (11). The study included consecutive 62 patients with CS. Among 36 texture parameters, high gray-level run emphasis (HGRE), which is a type of gray-level run length matrix, was selected as the best predictor of major adverse cardiac events (MACE). An HGRE value ≥1,000 was significantly associated with a poor outcome. A high HGRE value indicates that there are many high gray-level runs regardless of the length of the run. This result suggests that the heterogeneity of inflammatory activity based on the spatial distribution and intensity was clearly quantified by the TA. This retrospective study included a relatively small number of patients. Further studies of larger numbers of CS patients are warranted to validate the clinical role of a texture analysis using FDG PET.

**Phase analysis**

An evolving technique for measuring LV mechanical dyssynchrony is a phase analysis using electrocardiography (ECG)-gated single-photon emission computed tomography (SPECT) perfusion imaging. With this technique, the gated short-axis images are reconstructed to obtain the regional maximum counts from each temporal frame. Fourier transform is applied for a time-activity curve to estimate the timing of LV systole as demonstrated by the histogram. The phase

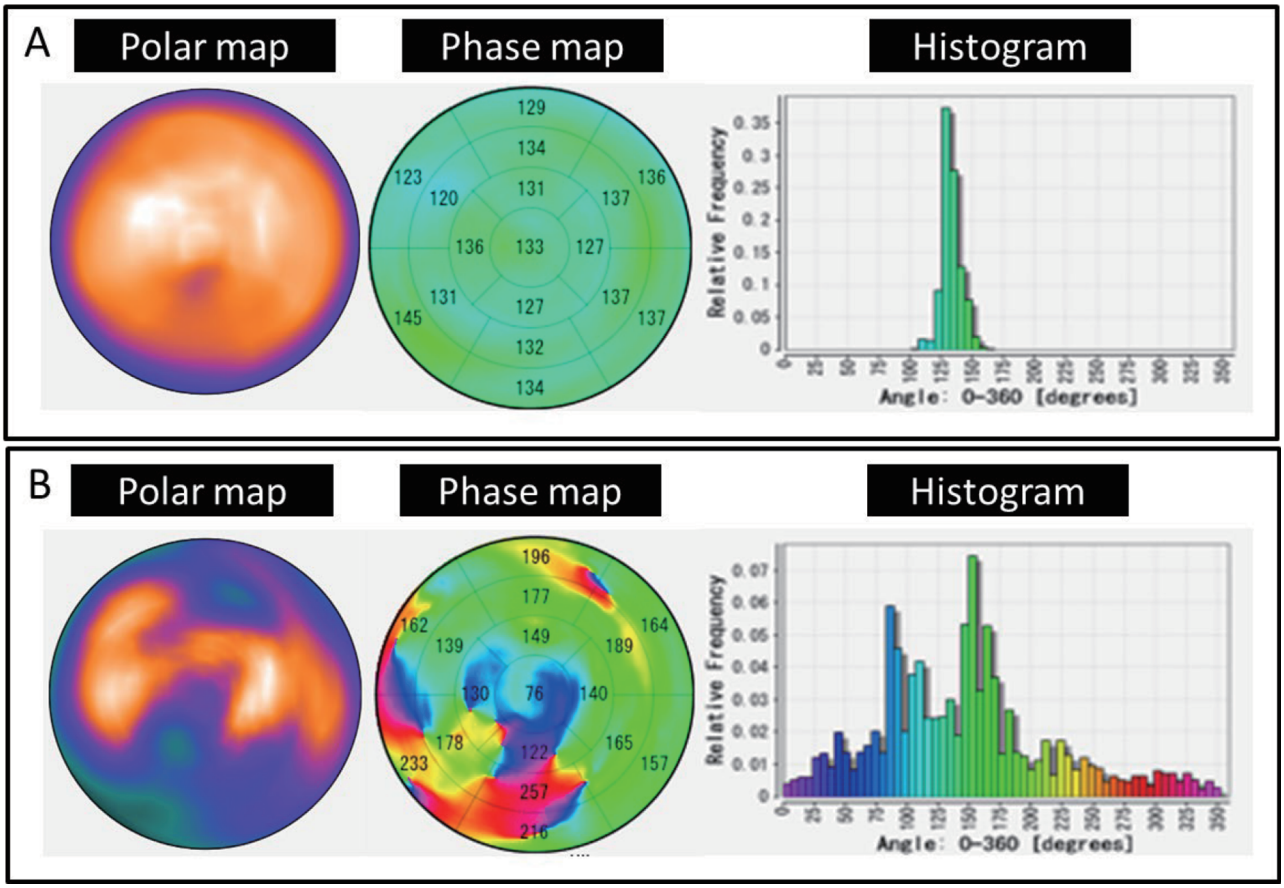


**Figure 2** Phase analysis using SPECT perfusion imaging. Fourier transform was applied for the time-activity curve to estimate the timing of LV systole as demonstrated by the histogram. Case A had normal perfusion and normal entropy＝36 (%), phase SD＝7 (°), and bandwidth＝28 (°) estimated by the histogram. Case B was a patient with severe multiple perfusion defects and high dispersion of the histogram of the phase analysis with high bandwidth: entropy=78 (%), phase SD= 81 (°), bandwidth=327 (°).

standard deviation (PSD), which is the standard deviation of the onset of the mechanical contraction phase, and the phase histogram bandwidth (BW), which is expressed as the 95% width of the phase histogram, are the representative parameters to assess LV global mechanical dyssynchrony (Figure. 2). Our study demonstrated that the MACE-free rate values can be stratified at the median of BW into the high-BW group (>56°) and the low-BW group (≤56°) (2). High BW was significantly associated with poor outcome.

**RV assessment**

The evaluation of the right ventricle's FDG uptake provides helpful information because the physiological FDG uptake of an RV is rare compared to such uptake in the LV (Figure. 1). The importance of RV assessment to evaluate the disease severity of CS has also been recognized. We recently evaluated 28 patients who underwent an endomyocardial biopsy (EMB) among 70 consecutive CS patients (12). Among the 28 patients with CS, a positive EMB result was detected in six patients (21%). This positive rate is almost the same as that reported in a 2008 Scientific Statement (13). However, when we focused on the RV uptake, the results revealed that the patients with positive RV FDG uptake had a significantly higher frequency of positive EMB results. This finding suggests that RV involvement indicates the spread of disease activity into the whole heart so that the rate of positive biopsy results was high. In terms of MACE, RV FDG uptake was more frequently associated with poor outcome compared to negative RV FDG uptake.

**Digital PET/CT**

A digital PET/CT scanner has high spatial resolution compared to analog PET/CT scanners (14). This high resolution can improve the detection of patchy sarcoidosis lesions in the heart, which is similar to the ability of cardiac MRI. MRI delayed enhancement shows multiple lesions including those in the RV wall, transmural enhancement in the anterior wall, and epicardial and endocardial enhancement in the lateral wall and septum. Regarding the lateral wall, digital PET clearly delineates epicardial and endocardial lesions at this site, similarly to MRI.

## Conclusion

The progress in image interpretation continues to overcome the limitations of diagnoses and risk stratifications provided by the conventional visual assessments of FDG PET and perfusion SPECT in patients with CS. Our recent efforts illustrate another valuable method that can be used to further advance artificial intelligence-guided diagnoses.

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## Conflicts of interest

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