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Qualitative and Quantitative Assessments of Cardiac Sarcoidosis Using ^{18}F-FDG PET

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Abstract

Sarcoidosis is a multisystem disease pathologically characterized by non-caseating granuloma. Cardiac sarcoidosis (CS) remains an important prognostic factor of sarcoidosis patients. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) has been applied as a noninvasive tool not only for CS diagnoses but also for the evaluation of therapeutic effects and prognoses. Visual assessment is a standard method to evaluate whether the ^{18}F-FDG uptake is physiological or active inflammation due to the CS. A semi-quantitative assessment using the standardized uptake value (SUV) is a simple method for achieving a more accurate diagnosis. A volume-based analysis has been proposed as a new marker that can provide information about the improvement or prevention of heart failure and can be used to predict a further clinical event in CS patients. This is a brief review of the objective and quantitative assessments of the magnitude and extent of CS activity with the use of ^{18}F-FDG PET.

Keywords: ^{18}F-fluorodeoxyglucose, Cardiac metabolic volume, Cardiac PET, Cardiac sarcoidosis, Inflammation
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Sarcoidosis is a multisystem disease pathologically characterized by non-caseating granuloma. Cardiac involvement remains an important prognostic factor for sarcoidosis patients (1), and the definitive and accurate diagnosis of cardiac sarcoidosis (CS) is thus warranted. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) has been used as a noninvasive approach not only for CS diagnoses but also for the evaluation of therapeutic effects and prognoses (2). The following is a brief review of the objective and quantitative assessments of CS using ^{18}F-FDG PET.

Visual assessment

^{18}F-FDG is an analog of glucose used as a marker of glucose metabolism. ^{18}F-FDG uptake in the inflammatory lesion is due to the activation of inflammatory cells such as neutrophil, monocytes, macrophages and so on with increased expression of glucose transporters and hexokinase. Therefore, sarcoidosis lesion with active inflammation can be visualized as obvious ^{18}F-FDG accumulation.

For the visual analysis of ^{18}F-FDG uptake patterns, Morooka et al. proposed a visual four-point scale of cardiac ^{18}F-FDG uptake compared to the hepatic uptake: (i) lower than the hepatic uptake, (ii) similar to the hepatic uptake, (iii) somewhat higher than the hepatic uptake, and (iv) notably higher than the hepatic uptake (3).

In the most common classification of cardiac ^{18}F-FDG accumulation, uptake patterns are divided into four groups based on a visual analysis: (i) without myocardial ^{18}F-FDG uptake, (ii) definite diffuse uptake in the entire left ventricle

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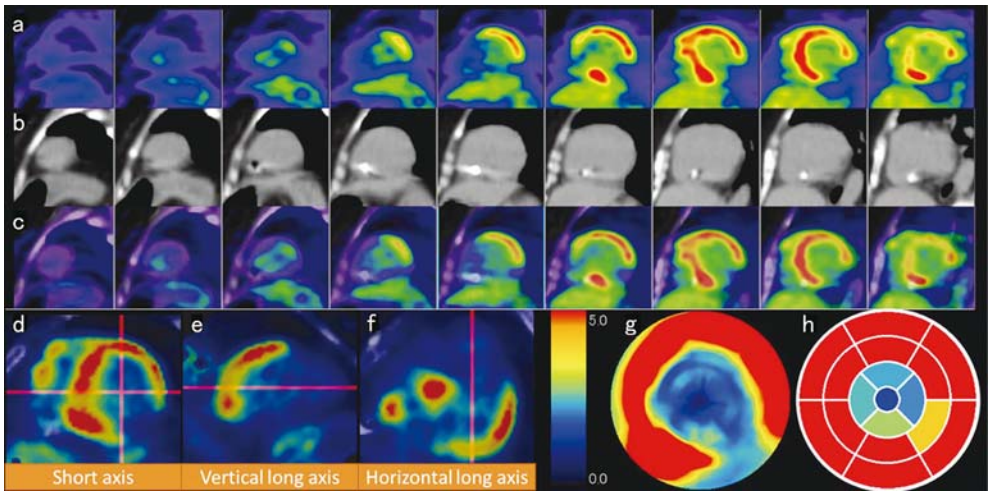

Fig. 1 Polar map and 17-segment model of cardiac ^{18}F-FDG uptake. Short-axis images of an ^{18}F-FDG PET (**a**), CT (**b**), and fused PET/CT image (**c**) are displayed on the upper panel. Noticeably high uptake is seen at the mid- to basal level of the left ventricle except for the inferior to inferolateral wall. There is also focal uptake on the right ventricle due to the patient's active cardiac sarcoidosis. Fused images (**d-f**) are useful to make a polar map (**g**) and to display the SUVmax in a 17-segment model.

(LV) wall, (iii) focal uptake, and (iv) focal on diffuse ^{18}F-FDG uptake in the LV wall (4). This four group classification was initially proposed by Ishimaru et al. and was also addressed in the Japanese Society of Nuclear Cardiology Imaging guidelines (5, 6). In addition, a 'diffuse at base' uptake pattern was often associated with inadequate suppression of physiological uptake. This pattern should also be carefully interpreted when examining the ^{18}F-FDG PET images of CS patients (7). Morooka et al. also reported that a diffuse uptake or basal ring-like and/or lateral uptake to be physiological in patients with suspected or known CS (3). Clinical information such as the electrocardiogram abnormality with conduction abnormalities, ventricular arrhythmia, serum free fatty acid value at the injection of ^{18}F-FDG and presence of extra-CS supported whether the uptake was physiological or not (3, 8, 9). Of course, multi-modality imaging combined late gadolinium enhancement of MRI, perfusion imaging and ^{123}I-BMIPP SPECT was useful to assess the active inflammatory processes and myocardial damage in patients with CS (10, 11). The physiological myocardial ^{18}F-FDG uptake may sometimes make it difficult to evaluate FDG PET imaging in sarcoidosis. The inter-observer agreement of cardiac ^{18}F-FDG uptake image patterns was improved by detailed pre-scan dietary preparation (12).

^{18}F-FDG uptake is expected to be useful not only to diagnose but also to predict the cardiac events related to CS. For example, in their study of 118 consecutive patients suspected of having CS, Blankstein et al. reported that the presence of increased ^{18}F-FDG uptake and a perfusion defect were associated with an increased risk of cardiac death or ventricular arrhythmia (13).

A 17-segment model following a statement from the American Heart Association is used to assess the distribution of ^{18}F-FDG uptake (Fig. 1). The location of ^{18}F-FDG uptake is of course important to assess CS. In particular, focal ^{18}F-FDG uptake in the interventricular septum was associated with atrioventricular (AV) block (9).

Because the physiological ^{18}F-FDG uptake of the right ventricle (RV) is observed less frequently compared to such uptake in the LV, the evaluation of the RV's ^{18}F-FDG uptake provides helpful information. ^{18}F-FDG PET has demonstrated that RV involvement is less frequent in CS than LV involvement. However, patients who had RV ^{18}F-FDG uptake showed a greater number of LV-involved segments (14) , and RV ^{18}F-FDG uptake was associated with subsequent death or ventricular tachycardia (VT) (13). Right ventricular ^{18}F-FDG uptake is thus also expected to be useful in diagnosing cardiac involvement and predicting cardiac events.

Semi-quantitative analysis

The use of the standardized uptake value (SUV) is now a common semi-quantitative method in clinical practice for evaluating the disease activity and monitoring the patient's response to therapy. The SUV is defined as the tissue activity concentration divided by the injected dose and the patient's body weight. The maximum SUV (SUVmax) of the whole heart or the 17 segments of the LV is frequently used because these values are simple to estimate. The SUVmax of a cardiac lesion is measured using a volume of interest inserted on the fused axial image encompassing the entire heart, followed by a review to ensure that adjacent non-cardiac ^{18}F-FDG-avid structures are excluded. An image fused with computed tomography (CT) morphologic information helps to divide the cardiac ^{18}F-FDG uptake into 17 segments if there is no positive

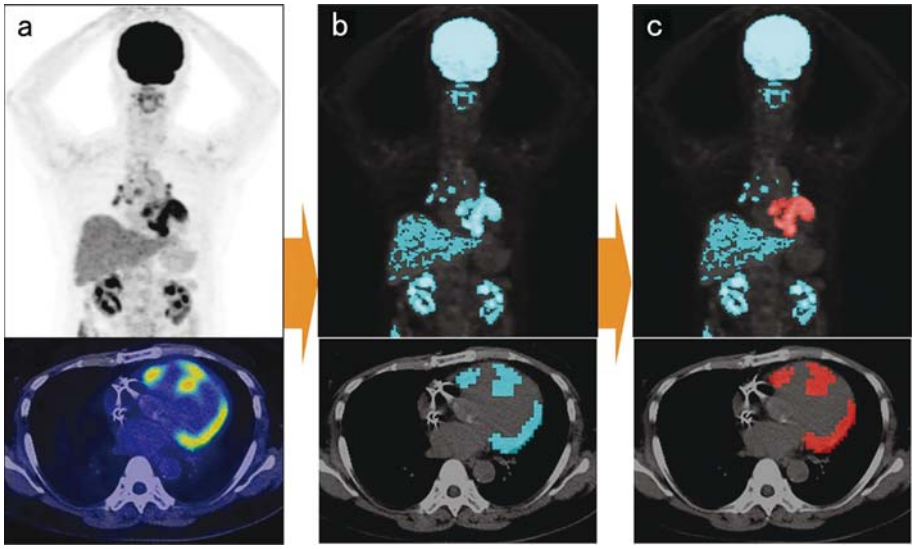

Fig. 2 Volume-based analysis of ^{18}F-FDG PET. A maximum intensity projection (MIP) image of ^{18}F-FDG PET and an axial image of PET/CT are presented (**a**). All of the voxels with an SUV over the defined threshold (on this occasion we used 1.5 times the SUVmax in the aortic blood pool) are visualized as the aqua color (**b**). The contoured margin(s) at the cardiac region (red color) were selected and reviewed to ensure that adjacent non-cardiac ^{18}F-FDG-avid structures were excluded (**c**). The cardiac metabolic volume (CMV) was calculated as the volume of the region of interest. The cardiac metabolic activity (CMA) was calculated by multiplying the CMV by the corresponding average SUV. In this case, the CMV was 87.2 ml and the CMA was 423.5 ml.

uptake segment.

McArdle et al. reported that there may be a relationship between the degree of ^{18}F-FDG uptake and the clinical presentation (particularly that of VT), because both the SUVmax and the maximum mean segmental SUV were significantly higher in CS patients with ventricular tachyarrhythmia compared to those with advanced AV block and compared to clinically silent CS patients (2). Yokoyama et al. demonstrated that the myocardial SUVmax was significantly higher in patients with CS compared to non-CS patients in the condition of overnight fasting (over 18 hours) followed a low-carbohydrate diet (15). Higher diagnostic accuracy compared to a visual analysis can be obtained using semi-quantitative methodology. Tahara et al. calculated the average, standard deviation, and coefficient of variation (COV) of the SUV among 17 segments of cardiac ^{18}F-FDG uptake (16). They reported that the average of the SUV showed no significant difference; however the standard deviation and COV in the CS patients were significantly higher compared to those of the controls, the non-CS patients, and dilated cardiomyopathy patients. Therefore, the identification of the heterogeneity of myocardial ^{18}F-FDG uptake may be a useful diagnostic marker of CS.

Volume-based analysis

The SUVmax reflects the value of a single voxel and thus does not account for the metabolism of the entire distribution of a target lesion. A volume-based analysis of parameters measured by ^{18}F-FDG PET such as those of the metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have emerged as new assessment tools, mainly for assessing malignant tumors. The cardiac metabolic volume (CMV) is similar in concept to the MTV, and is measured by contouring margins defined by thresholds such as the liver uptake, the blood pool SUV, the fixed value of SUV, or the %uptake of the SUVmax (8, 17). The cardiac metabolic activity (CMA) is calculated by multiplying the CMV by the corresponding average SUV, which is similar in concept to the TLG (Fig. 2) (18). Osborne et al. reported that the reduction of the SUVmax and CMV in a comparison of pre- and post-therapy values was associated with improvement in the left ventricular ejection fraction (LVEF), which suggested that serial PET scanning might help guide the titration of immunosuppressive therapy to improve LV function or prevent heart failure in CS (19). Ahmadian et al. demonstrated that the CMA was greater in patients with lower LVEF and preceding adverse clinical events such as VT, sudden cardiac death, and heart block (18). In addition, CMA was the only independent predictor of events including ventricular tachycardia (VT), sudden cardiac death, worsening atrio-ventricular block, cardiac hospitalization and new or worsening heart failure using binary logistic regression analysis with CMA, SUVmax and total defect score of perfusion image. A volume-based analysis using ^{18}F-FDG PET might become a tool for guiding the titration of immunosuppressive therapy and predicting cardiac events.

Conclusion

We have briefly reviewed objective and quantitative assessments of cardiac sarcoidosis using ^{18}F-FDG PET. Visual assessment is a standard method to evaluate the presence of

abnormal ^{18}F-FDG uptake by active inflammation. The semi-quantitative method using the SUV is a simple way to aid the visual assessment to achieve a more accurate diagnosis. Although performing a volume-based analysis is not always easy in clinical settings, such an analysis provides information that can be used to predict clinical events. In addition, the SUV and a volume-based analysis might be useful for the objective monitoring of the patient response to immunosuppressive treatment.

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Conflicts of interest

All authors have no conflict of interest.

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References

1. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med 2007; 357: 2153-65.
2. Mc Ardle BA, Birnie DH, Klein R, et al. Is there an association between clinical presentation and the location and extent of myocardial involvement of cardiac sarcoidosis as assessed by ^{18}F-fluorodoexyglucose positron emission tomography? Circ Cardiovasc imaging 2013; 6: 617-26.
3. Morooka M, Moroi M, Uno K, et al. Long fasting is effective in inhibiting physiological myocardial ^{18}F-FDG uptake and for evaluating active lesions of cardiac sarcoidosis. EJNMMI Res 2014; 4: 1.
4. Yoshinaga K, Manabe O, Ohira H, et al. Focus issue on cardiac sarcoidosis from international congress of nuclear cardiology and cardiac CT (ICNC 12) symposium: improving the detectability of cardiac sarcoidosis − practical aspects of ^{18}F-fluorodeoxyglucose positron emission tomography imaging for diagnosis of cardiac sarcoidosis −. Ann Nucl Cardiol 2016; 1(1): 87-94.
5. Ishimaru S, Tsujino I, Takei T, et al. Focal uptake on ^{18}F-fluoro-2-deoxyglucose positron emission tomography images indicates cardiac involvement of sarcoidosis. Eur Heart J 2005; 26: 1538-43.
6. Ishida Y, Yoshinaga K, Miyagawa M, et al. Recommendations for ^{18}F-fluorodeoxyglucose positron emission tomography imaging for cardiac sarcoidosis: Japanese Society of Nuclear Cardiology recommendations. Ann Nucl Med 2014; 28: 393-403.
7. Ito K, Okazaki O, Morooka M, et al. Visual findings of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography in patients with cardiac sarcoidosis. Intern Med 2014; 53: 2041-9.
8. Manabe O, Yoshinaga K, Ohira H, et al. The effects of 18-h fasting with low-carbohydrate diet preparation on suppressed physiological myocardial ^{18}F-fluorodeoxyglucose (FDG) uptake and possible minimal effects of unfractionated heparin use in patients with suspected cardiac involvement sarcoidosis. J Nucl Cardiol 2016; 23: 244-52.
9. Manabe O, Ohira H, Yoshinaga K, et al. Elevated ^{18}F-fluorodeoxyglucose uptake in the interventricular septum is associated with atrioventricular block in patients with suspected cardiac involvement sarcoidosis. Eur J Nucl Med Mol Imaging 2013; 40: 1558-66.
10. Kataoka S, Momose M, Fukushima K, et al. Regional myocardial damage and active inflammation in patients with cardiac sarcoidosis detected by non-invasive multi-modal imaging. Ann Nucl Med 2017; 31: 135-43.
11. Manabe O, Oyama-Manabe N, Ohira H, et al. Multimodality evaluation of cardiac sarcoidosis. J Nucl Cardiol 2012; 19: 621-4.
12. Ohira H, Mc Ardle B, deKemp R, et al. Inter- and Intra-observer agreement of FDG-PET/CT image interpretation in patients referred for assessment of Cardiac Sarcoidosis. J Nucl Med 2017. doi: 10.2967/jnumed.116.187203. [Epub ahead of print]
13. Blankstein R, Osborne M, Naya M, et al. Cardiac positron emission tomography enhances prognostic assessments of patients with suspected cardiac sarcoidosis. J Am Coll Cardiol 2014; 63: 329-36.
14. Manabe O, Yoshinaga K, Ohira H, et al. Right ventricular ^{18}F-FDG uptake is an important indicator for cardiac involvement in patients with suspected cardiac sarcoidosis. Ann Nucl Med 2014; 28: 656-63.
15. Yokoyama R, Miyagawa M, Okayama H, et al. Quantitative analysis of myocardial ^{18}F-fluorodeoxyglucose uptake by PET/CT for detection of cardiac sarcoidosis. Int J Cardiol 2015; 195: 180-7.
16. Tahara N, Tahara A, Nitta Y, et al. Heterogeneous myocardial FDG uptake and the disease activity in cardiac sarcoidosis. JACC Cardiovasc imaging 2010; 3: 1219-28.
17. Hirata K, Kobayashi K, Wong KP, et al. A semi-automated technique determining the liver standardized uptake value reference for tumor delineation in FDG PET-CT. PloS One 2014; 9: e105682.
18. Ahmadian A, Brogan A, Berman J, et al. Quantitative interpretation of FDG PET/CT with myocardial perfusion imaging increases diagnostic information in the evaluation of cardiac sarcoidosis. J Nucl Cardiol 2014; 21: 925-39.
19. Osborne MT, Hulten EA, Singh A, et al. Reduction in ^{18}F-fluorodeoxyglucose uptake on serial cardiac positron emission tomography is associated with improved left ventricular ejection fraction in patients with cardiac sarcoidosis. J Nucl Cardiol 2014; 21: 166-74.