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Optimal Patient Preparation for Detection and Assessment of Cardiac Sarcoidosis by FDG-PET

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Abstract

Abnormal uptake of ^{18}F-fluorodeoxyglucose (FDG) in the heart on positron emission tomography (PET) was recently included in the major criteria of diagnostic guidelines for cardiac sarcoidosis (CS). The high sensitivity but great variability in specificity in the diagnosis probably due to variable preparation methodologies of FDG-PET was reported. There are three main methods which have been reported to minimize physiological FDG uptake in the normal myocardium. A low carbohydrate diet on the day before PET with an overnight fasting more than 18-h achieves almost complete suppression of myocardial FDG uptake. Use of heparin pre-injection or high-fat diet preparation may enhance the suppressive effect. Serum FFA levels before PET imaging might be a biomarker of predicting the physiological FDG uptake in the myocardium.

Keywords: Cardiac sarcoidosis, FDG-PET, Free fatty acid, Low carbohydrate diet
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Abnormal uptake of ^{18}F-fluorodeoxyglucose (FDG) in the heart on positron emission tomography (PET) was finally included in the major criteria of diagnostic guidelines for cardiac sarcoidosis (CS) by the Japanese Society of Sarcoidosis and other Granulomatous Disorders in 2015 (1). In 2012, the Japanese Ministry of Health, Labor and Welfare (JMHLW) had approved reimbursement coverage for FDG-PET usage to detect inflammation sites in CS firstly in the world. However, there was no standard for or consensus on the preparation and image interpretation for FDG-PET/CT.

Thus, the guidelines for FDG-PET imaging for CS were published by the Japanese Society of Nuclear Cardiology in 2014 (2). In the guidelines, more than 50 articles in the field were reviewed and the high sensitivity but great variability in specificity in the diagnosis of CS probably due to variable preparation methodologies of FDG-PET was reported. This review tries to update an optimal patient preparation for detection and assessment of CS by FDG-PET.

Conceptual background

More than 90% of fasting myocardial energy metabolism in humans is due to fatty acid. The remaining less than 10% of metabolism involves other substances including glucose (3). However, myocardial FDG uptake is observed even under fasting conditions in some cases. An inhibitory effect of FFA on glucose uptake in the perfused rat heart was firstly reported by Randle et al. (4). Then, Nuutila et al. demonstrated by FDG-PET that elevation of serum FFA inhibits glucose uptake in the heart and skeletal muscles in humans (5). Glucose utilization in myocardial cells is enhanced in the presence of increased blood glucose and insulin levels after a meal, whereas it is suppressed as serum FFA levels increase during continued fasting (6). This suppression is mediated by insulin-dependent Type 4 cellular glucose transporter (GLUT4) (Fig. 1a).

On the other hand, inflammation associated cells, such as neutrophils, monocytes, and macrophages, express high levels of GLUT1 and GLUT3 in the cell membrane (6, 7). Hence,

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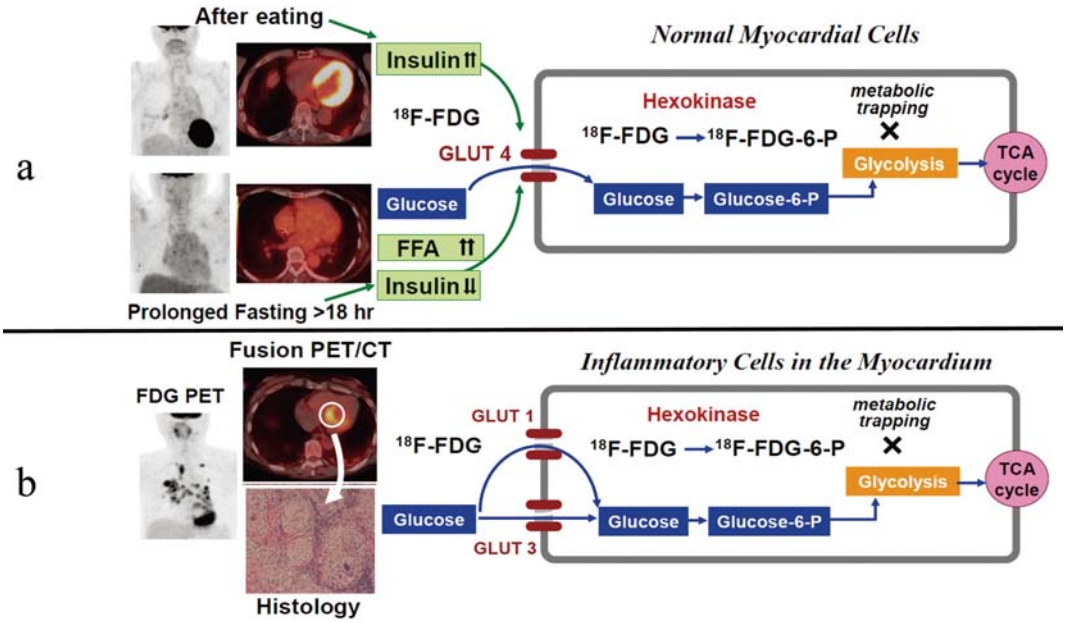

Fig. 1a Randle cycle.

After eating, ^{18}F-fluorodeoxyglucose (FDG) PET/CT images of a normal volunteer depict diffuse FDG accumulation in the left ventricular myocardium. Prolonged overnight fasting > 18-h, there is no accumulation in the myocardium. Glucose utilization in the normal myocardial cells is enhanced in the increased blood insulin levels after eating. In contrast, it is suppressed as serum free fatty acid (FFA) levels increase during a continued fasting state.

Fig. 1b PET/CT images of a patient with cardiac sarcoidosis (CS).

Increased accumulation of FDG is shown in the multiple hilar and mediastinal lymph nodes and the heart. PET/CT depicts focal accumulation of FDG (white circle) in the interventricular septum. CS was confirmed by biopsy. In the inflammatory cells, cellular activation increases both GLUT1 and GLUT3 but not GLUT4 expression. ^{18}F-FDG-6-P: FDG-6-phosphate, Glucose-6-P: glucose-6-phosphate, GLUT: glucose transporter protein, TCA: tricarboxylic acid cycle

separately visualizing FDG uptake in CS lesions through GLUT1/GLUT3 is possible if GLUT4 is adequately suppressed in normal myocardial cells (Fig. 1b).

How to minimize physiological FDG uptake in the normal myocardium

1. Extended fasting duration before FDG-PET

To date in the literature, there are three main methods to minimize physiological FDG uptake in the normal myocardium. In the first place to do is to prolong intervals of fasting, which may lead to a decrease in blood glucose and insulin levels and, eventually, an increase in blood FFA levels. Most of the papers reviewed in the Guideline discussed fasting conditions in more than 12 hours (2). Attention is paid to the high sensitivities, but the low specificity and high variability are also highlighted. Recently, several studies confirmed that more than 18-h of fasting made an improvement in specificity. (8-11).

We measured the maximum standardized uptake value (SUVmax) in the myocardium on 215 consecutive FDG-PET/CT at different fasting duration with no dietary modification (12), and also found that SUVmax in the myocardium is significantly reduced only in the group of patients with more than 18-h overnight fasting (Fig. 2).

2. Dietary modification prior to FDG-PET

In the second place to do is dietary modification prior to FDG-PET. A low-carbohydrate diet (LCD) ＜5 g the night before FDG PET is highly recommended to minimize blood glucose and insulin levels (13, 14). Coulden et al. reported that an Atkins-style LCD (less than 3 g) on the day before PET together with an overnight fasting effectively suppresses myocardial FDG uptake than the overnight fasting alone. Myocardial SUVmax fell from 3.53 ± 2.91 of controls to 1.77 ± 0.91 of patients with LCD.

Additionally, a LCD together with a high-fat diet 3-6 h before PET was also recommended to suppress physiological FDG uptake in the myocardium (15). However, the efficacy of high-fat diet by itself in increasing serum FFA levels has yet to be established. Cheng et al. randomized 63 outpatients referred for oncologic FDG-PET to high-fat low-carbohydrate (HFLC), LC, or unrestricted (UR) dietary preparations starting the evening before PET. HFLC patients drank a fatty drink 60-70 minutes prior to FDG injection. They concluded that using UR patients as reference, myocardial SUVmax was lower in LC patients but not in HFLC patients (16).

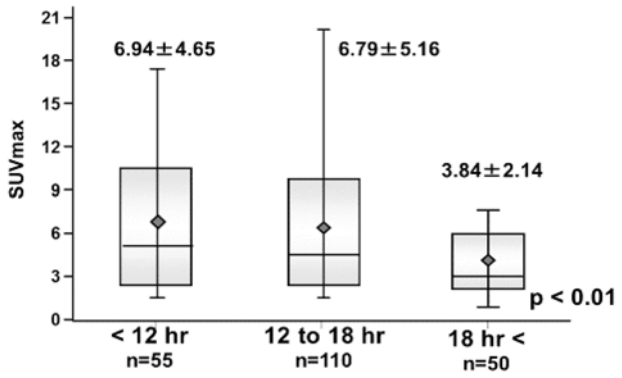

Fig. 2 Relationship between fasting duration and standardized uptake value (SUVmax) in the myocardium on oncology FDG PET/CT.

Consecutive 215 oncology patients were measured the maximum SUVmax in the myocardium on FDG PET/CT at different fasting duration. SUVmax in the myocardium is significantly reduced only in the group of patients with more than 18-h overnight fasting.

Demeure et al. conducted a similar randomized trial (17). 36 volunteers who ate a HFLC meal, followed by a 12-h fasting period, then, they were randomized to two groups: one with no additional preparation and the other who received a high-fat solution containing 43.8 g of lipids or 50 mL of olive oil 1-h before FDG injection. Myocardial SUVmax did not significantly differ between two groups. A HFLC meal followed by a 12-h fasting period effectively suppressed myocardial FDG uptake in most subjects. However, complementary fatty acid loading 1-h before FDG injection derived no additional benefit.

Interestingly, serum FFA levels were higher in volunteers with good suppression than in those with poor suppression (P=0.011). An inverse correlation between serum FFA level and the SUVmax (R=0.61) was found, which may represent a method to predict myocardial FDG uptake suppression.

3. Pre-administration of unfractionated heparin

In the last place, pre-administration of unfractionated heparin activates the serum lipoprotein lipase to increase FFA, resulting suppression of myocardial glucose utilization. The protocol for intravenous injection of heparin at a dose of 50 IU/kg, 15 min prior to FDG administration has been adopted, which increases serum FFA levels rapidly after heparin injection (9-11, 18-19). On the other hand, although subject's body weights were not mentioned. There are very few reports examining the relationship between the dose of heparin and the suppression of myocardial FDG uptake.

Scholtens et al. (19) compared FDG-PET scans between two protocols of LCD plus 12-h fasting, and LCD plus 12-h fasting together with 50 IU/kg heparin injection. Heparin injection in addition to a LCD plus 12-h fasting significantly outperforms that without injection. Nevertheless, inadequate cardiac suppression is still found in 12% of patients after LCD plus 12-h fasting together with heparin injection.

Subsequently, Morooka et al. (9) confirmed that an 18-h fasting without LCD is more effective for inhibiting physiological myocardial uptake than a 12-h fasting together with heparin injection in patients with known or suspected CS. They also suggested that serum FFA level before heparin injection may be the key factor in inhibiting physiological FDG uptake. It was likely to be efficiently inhibited when the serum FFA level was >760 μEq/L.

Finally, Manabe et al. (10) stated that a LCD with a minimum 18-h fasting together with 50 IU/kg heparin pre-injection completely suppressed physiological FDG uptake in 24 patients. On the other hand, 16 of 58 patients (27.6%) with a minimum 6-h fast without LCD preparation showed diffuse myocardial uptake. The former group showed higher serum FFA (1,159 ± 393 vs. 651 ± 311 μEq/L, P<0.0001) than did the latter group before heparin injection. Although serum FFA significantly increased in both groups 15 minutes after heparin injection (P<0.0001), there were no significant difference in FFA levels between two groups (2,116 ± 531 vs. 2,026 ± 712 μEq/L, respectively).

Care must be taken to prevent the occurrence of heparin-induced thrombocytopenia (HIT). The incidence of HIT has been reported to vary from 0.5 to 5% (20). Heparin administration is contraindicated in patients with a known bleeding tendency. In addition, it is reported that preceding exposure to heparin can lead to the formation of HIT antibodies. Patients can develop immune heparin-induced thrombocytopenia in the second exposure even very small amount of heparin (21, 22). We do not have enough data regarding an appropriate dose and regimen of heparin injection at this moment. Future studies comparing different doses and regimen are needed.

Conclusion

The LCD on the day before FDG PET together with an overnight fasting more than 18-h achieves almost complete suppression of physiological FDG uptake in the myocardium. The use of heparin pre-injection or high-fat diet preparation may enhance the suppressive effect. In addition, serum FFA levels before PET imaging might be a biomarker of predicting the physiological FDG uptake in the myocardium.

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Conflicts of interest

None declared.

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