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The Effect of Fasting on Positron Emission Tomography (PET) Imaging: *A Narrative Review*

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ABSTRACT

As a nuclear approach, Positron Emission Tomography (PET) is a functional imaging technique which is based on the detection of gamma ray pairs emitted by a positron-emitting radionuclide. There are certain limitations to this technique such as normal tissue uptake. Therefore, it has been recommended that patients prepare before scanning. Fasting for a short while before PET imaging is an example of such preparation.
In this paper, we attempted to collect the studies evaluating the effects of fasting in the three sections of cardiac, brain and abdominal PET imaging. Conclusively, we found that the effects of fasting on PET imaging can be different depending on the type of PET scanning, radiotracer, patient's diseases, fasting duration and in case of any additional dietary plans. It is proposed that further study be conducted on this subject in order to determine such effects in more detail.

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Introduction

The three-dimensional images of the functional processes occurred in the body were provided after the introduction of Positron Emission Tomography (PET) as a nuclear functional imaging technique over two decades ago (1, 2). This technique involves the detection of gamma ray pairs indirectly emitted by a positron-emitting radionuclide (tracer), which is administered into the body on a biologically active molecule. Afterwards, the three-dimensional images of the tracer distribution inside the body are constructed through computerized analysis(3).

Radionuclides used in PET scanning are usually isotopes with a short half-life; such examples are fluorine-18 (~110 min), carbon-11(~20 min), nitrogen-13 (~10 min), oxygen-15 (~2 min),or rubidium-82(~1.27 min). These radionuclides are either incorporated into the compounds which are normally consumed by the tissues such as glucose (or glucose analogues), water, or ammonia, or they are incorporated into the molecules which bind to receptors or other sites of the active drugs (4).

Up to now, one of the most frequently used radiotracers in the clinical PET scanning is an analogue of glucose and Fluorodeoxyglucose (FDG) labeled with fluorine-18. This radiotracer is also utilized in oncology and several neurology scans (5).

PET is widely applied in the other medical fields such as clinical oncology (medical imaging of tumors and search for metastases), neuroimaging, cardiology, pharmacokinetics, treatment of brain diseases and small animal imaging (6).

The spatial resolution of PET is relatively low in comparison to other imaging modalities (7). This is due to several factors such as annihilation photon non-collinearity, positron range, under-sampling of the signal in the linear or angular directions for the image reconstruction process and the patient's motion (2, 7, 8).

As a result, designing a protocol to overcome this limitations is a critical issue. Many studies have attempted to improve the spatial resolution of PET through combining PET images with CT-scan or MR images, using lutetium oxyorthosilicate (LSO) or Bismuth

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germanate (BGO) detectors in order to enhance the counting-rate capabilities, or applying particular image reconstruction programs (3, 9, 10).

On the other hand, with the reduction of the tracer uptake in normal tissues (kidneys, bladder, skeletal muscle, myocardium, and brown fat), maintaining and optimizing tracer uptake in the target structures (tumor tissue) could enhance the quality of PET images. To achieve this goal, several studies have proposed protocols to prepare patients before scanning. Nutritional restrictions like fasting are an example of such preparations which do not allow patients to consume any food or sugar for at least 6 hours prior to PET scan (8).

The present review aimed to compare the results of a few studies recently conducted about the effects of fasting on the function of important organs such as myocardium, brain, liver or even cancerous tumors as well as to compare PET images in normal patients and those who were fasting before the scanning.

The effect of fasting on cardiac PET scan

F-18-2-fluoro-2-deoxyglucose (F-18 FDG), a glucose analog PET radiotracer, is routinely used in cardiology for evaluating myocardial feasibility and cardiovascular diseases such as cardiac sarcoidosis and myocarditis (11, 12). F-18 FDG is elated within the myocytes undergoing phosphorylation by FDG-6-phosphate where no additional metabolism occurs (12). The considerable physiological accumulation of FDG in the myocardium could be interfered with the detection of abnormal FDG uptake (13).

Cardiac metabolism is a complex phenomenon. In normal myocardium, oxidative metabolism is the primary source of energy utilizing free fatty acids (FFA), glucose, and lactate as substrates. Myocyte glycolysis is a variable dependent upon several factors including diet, the accessibility of FFAs, medications, presence or absence of diabetes, serum insulin levels, serum glucose concentration and the duration of fasting (14, 15).

In the fasting state, the FFAs act as the substrate of selection as the plasma insulin levels descend due to the smaller transfer of glucose into the myocytes (16-18). Alternatively, Hyperinsulinemia suppresses the serum concentration of FFAs causing the myocardial glucose removal to enhance. The amount of the glucose extracted and oxidized by the myocardium is inversely correlated with the arterial level of FFAs (14). Consequently, it is presumed that cardiac cells uptake might also be correlated with the fasting state.

In the studies attempting to evaluate the uniformity of myocardial accumulation of FDG in normal fasting individuals, it was indicated that normal human myocardium is likely to manifest significant regional disparities under a 5-hour fasting condition. In this process, the activity of the septum and anterior wall significantly decreases compared to the lateral and posterior walls (16, 19).

In their study, Gropler et al. claimed that the specificity of FDG imaging while detecting myocardial ischemia or any other medical conditions could be restrained if the scanning is performed in a state of fasting, unlike carbon-11-acetate radiotracer which induces homogenous accumulation and glucose loading conditions while fasting (16).

In 2002, Lum et al. realized that myocardial FDG uptake in PET would reduce if dietary carbohydrate restrictions were assigned to the patients. The examined patients were not allowed to consume any foods containing carbohydrates for 12 hours prior to the PET scan. It was suggested that the combination of pre-scan fasting in the patients undergoing FDG-PET scans could improve the evaluation of the neoplastic diseases of the thorax (20).

In another study in 2005, Groot et al. attempted to determine the effects of a 6-hour fasting period before whole-body FDG-PET scanning. The results indicated that fasting and blood glucose levels did not influence the physiological uptake (21). By contrast, Kaneta et al. in 2006 stated that FDG uptake in myocardium did not have any significant correlation with fasting. They also suggested that long periods of fasting, as in overnight fasting, was inadequate to reduce the physiological uptake of FDG in the heart (22).

In 2009, Cheng et al. evaluated the impact of carbohydrate restriction with and without fatty acid loading on the myocardial 18F-FDG uptake during PET. They emphasized the control of unwanted heart uptake in order to identify such

thoracic diseases as cardiac sarcoidosis and malignancies neighboring or infiltrating the cardiac chambers. In their randomized controlled trial, a low-carbohydrate diet with extended fasting resulted in the suppression of myocardial 18F-FDG uptake during PET. Thus, they suspected that the protocol could be useful in developing FDG-PET to probe coronary arterial inflammation (23).

In the same year, Langah et al. investigated the effectiveness of prolonged fasting 18F-FDG PET in the detection of cardiac sarcoidosis. They concluded that prolonged fasting (12 to 18 hours) could effectually reduce the levels of serum insulin and glucose and thus, suppress the physiologic myocardial glucose influx in the myocardium. Furthermore, their results indicated that prolonged fasting FDG PET/CT required a more sensitive and accurate imaging modality as to detect cardiac sarcoidosis in comparison with 67-Gallium scintigraphy. They also proposed that prolonged fasting and low serum are paramount in the proper interpretation of FDG PET/CT to detect cardiac sarcoidosis (14).

In 2011, Brancato et al. studied 22 patients with fasting FDG PET, sestamibi, SPECT and gallium scintigraphy reporting that PET had a far more elevated sensitivity compared to other imaging techniques (24).

In 2013, Kobayashi et al. suggested a method to suppress myocardial uptake of FDG which involved the administration of a low-carbohydrate, high-fat (LCHF) dietary supplement before the start of the procedure. They demonstrated that this protocol was likely to improve the value of FDG-PET/CT in the evaluation of myocardial inflammation (13).

In 2014, Thut et al. demonstrated that the myocardial FDG uptake while fasting for more than five hours was vastly variable albeit it was not significant. They indicated that fasting alone could not explicate the difference of myocardial metabolism and it depended on multifactor such as glucose and FFA levels as well as the levels of insulin, glucagon, epinephrine, dopamine and thyroxine in addition to other physiological and cellular procedures like myocardial blood flow and oxygen. They confirmed that the regional myocardial wall varied in prototype as the peak uptake of glucose could be seen which could not be explained by the length of fasting (15).

On the other hand, Kumar et al. evaluated 153 patients who were divided into three groups of A: patients fasting for 4 hours, B: patients fasting for 12 hours and C: patients of overnight fasting. All the subjects were on a low-carbohydrate and fat-rich diet for 2 days prior to the study. They concluded that myocardial uptake suppression was better when there was a combination of controlled diet and fasting than fasting alone (12). Similarly, Morooka et al. demonstrated that the physiological myocardial uptake was more proficiently inhibited in patients of the long-fasting group (18 hours) compared with the group who received Heparin injection (11).

In summary, we could infer that such factors as the length of fasting, diet restriction before the procedure and serum glucose and FFA could be of consequence in the accurate determination of some diseases.

The effect of fasting on brain PET scan

Glucose is the leading fuel of the brain providing almost 95% of the Adenosine 5′-triphosphate (ATP) required for brain function (8, 25). FDG PET is currently the most precise in-vivo technique to examine the regional human brain metabolism. In guidelines for the preparation of patients, it is suggested that they fast approximately 4 hours in advance for the optimal cerebral FDG uptake not to be influenced by enlarged serum glucose levels (8). Studies have shown insulin to have a significant effect on the global brain glucose metabolic rate, mainly in the cerebral cortex, via stimulating the glucose uptake and metabolism as well as the neuronal cells to increase glucose metabolism (26).

Activities in the cortico limbic reward systems change in reaction to the taste, smell, thought and the sight of food and feeding behaviors. Such functional neuro imaging techniques as PET are able to measure these changes. In 2009, Goldstone et al. claimed that fasting, in comparison with having breakfast, increased the activation of high-calorie components more than low-calorie foods in the ventral striatum, amygdala, anterior insula and medial and lateral orbitofrontal cortex (OFC) (27).

On the other hand, during a metabolic stress like fasting and starvation, Ketone bodies induce an enhancement of fatty acid oxidation while reducing glucose oxidation formed by the liver (28). Ketones (β-hydroxybutyrate and

acetoacetate) transform into acetoacetyl-CoA and acetyl-CoA in extra hepatic tissues like brain. Then, they enter the tricarboxylic acid pathway for ATP generation through the same final pathway as glucose (29).

There are accumulating evidences of the neuroprotective effects of Ketones in the form of anticonvulsant activity, protection against oxidative stress, diminishing the effects of acute brain injury and ischemic damage and anti-tumor effects on gliomas (28).

In 2009, Bentourkia et al. proposed that PET imaging can enhance the brain uptake of ketones approximately seven to eight fold during a Ketogenic diet or while fasting (29). Therefore, with the combination of PET technology and dietary conditions like fasting and using radiotracers (11C-acetoacetate), we can organize a non-invasive and quantitative method in order to investigate brain energy metabolism and brain ketone metabolism in a health human and patient.

The effect of fasting on abdominal PET imaging

Using FDG as a tracer, PET has been established as an efficient approach in the diagnosis and evaluation of many types of malignancies (30). However, it is of less value in the assessment of some disorders such as primary gastric malignancies and Hepatocellular carcinoma (HCC) if performed in a state of fasting (31, 32).

Gastric cancer is the world's fourth most prevalent malignancy (33) with a poor prognosis which is scheduled as the second principal cause of cancer mortality worldwide (30, 34). However, in clinical and scientific research, PET has been used extensively for the primary diagnosis of gastric cancer and preoperative staging and as a surgery guideline (33). Conventional FDG PET has limited value in detecting early stage tumors of the stomach, mostly because of the limitations in resolution, sensitivity and accuracy and the relatively high levels of physiological uptake by the contracted stomach (34, 35).

Intense 18F-FDG uptake in the stomach has been known to be independent of dietary differences being correlated with the richness in smooth muscles and digestive glands (31). Several studies have applied simple methods to increase the tumor/background ratio, even for small-size tumors. They have recommended that patients drink water or milk or have some food or foaming agents immediately before PET scanning as to effectively distend their stomach (30, 31, 33). This way, the gastric distention caused by the normal gastric wall uptake would be relatively lower whereas malignant lesions would not exhibit many changes in their appearance due to their low elasticity (31).

HCC is another common malignancy with a high mortality rate in the world and specifically in Asian countries (36). Although FDG PET is regarded as the most efficient modality for evaluating many kinds of tumors, applying FDG PET imaging to liver cancer is quite challenging (32, 37). The sensitivity of PET in the diagnosis of HCC was 55% compared to 90% in CT scanning (38). Furthermore, using other radiotracers such as 11C-acetate can result in a higher sensitivity and specificity complementary to 18F-FDG in the diagnosis of liver cancer(39).

In most studies, the patients prepared with 4-6 hours of fasting before scanning. Nevertheless, hardly any study has fully evaluated the effects of fasting on the qualitative and quantitative parameters of PET. Only Kolthammer et al. in 2011and Tenley in 2013 investigated the effects of fasting on the performance of Choline-based and acetate tracers in HCC PET imaging, respectively. They demonstrated that animal fasting did not have any significant correlation with tumor uptake and its effects could be negligible (32, 40).

Finally, fasting did not seem to affect the diagnosis of abdominal cancer, especially gastric and liver cancer. However, further investigations need to made in the form of studies to determine the effects of fasting in detail.

Conclusion

Although fasting is a common requirement in PET imaging, it seems to have various effects under different circumstances. The effect of fasting on PET imaging could alter depending on the type of PET scanning, radiotracer, patient's diseases, the duration of fasting and in case of any specific, additional dietary plans. This review indicated that to publish or update guidelines, details on the preparation of patients about the state of fasting need to be taken into account.

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