CHAPTER **42**

FLURODEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY: A New Technique to Evaluate Infectious Processes

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INTRODUCTION

Infection is a continuum, on one end of the spectrum you have uncomplicated skin and soft tissue infections that may resolve with local wound care. On the other end you have limb and life threatening infections that need to be dealt with emergently. The difficulty lies in the middle where infection and inflammation can often overlap. Flurodeoxyglucose (FDG) Positron Emission Tomography (PET) is a relative new technique that physicians can use diagnostically to identify the presence of an infection.

Traditionally, standard radiograph technology has been used in evaluating the presence of an infection; however, any acute osseous changes are seldom revealed on plain films until the infection has reached advance stages. Alterative methods of imaging are computed tomography (CT), magnetic resonance imaging (MRI), and nuclear medicine. CT, MRI and bone scans are modalities currently used to determine the presence of an infection. CT uses high-energy ionizing radiation and computers to generate images of standard anatomy. MRI uses radiofrequency pulses that are absorbed and readmitted by the patient inside a magnetic field. Nuclear medicine uses radioactive isotopes to evaluate physiological activities like PET imaging. However, it does not detect the presence of infection, but reflects the reaction of bone possibly associated with an infection.

CT and MRI provide excellent contrast resolution and have become the preferred modality for evaluating significant infections. The accuracy of MRI is being questioned when diagnosing infections where normal anatomy has been distorted. Basu et al in 2007 studied the accuracy of MRI diagnosis with histopathologic examinations, and found that MRI can not reliably distinguish osteomyelitis from marrow edema associated with other non-infectious processes, since the presence of a pathologic process alters normal tissue structure thus causing signal intensity to the anatomy area to change. FDG PET is a modality that is currently being utilized in the detection of complicated and uncomplicated infections. PET imaging or PET scanning is a type of diagnostic scintigraphy that involves detecting radiation from the emission of positrons to produce physiologic images.

HISTORY

PET imaging is a non-invasive radioactive technique that was first discovered by Michael E. Phelps at the Washington School of Medicine in 1975 and has since become established in the study of oncology, cardiology, neurology, and now podiatry (Figure 1). The initial onocologic study used PET imaging to diagnose, stage, and monitor the success of cancer therapy. These initial studies were in Hodgkin's lymphoma, Ewings Sarcoma, malignant melanoma, breast cancer, and variety of other cancers. Total body image results allow the clinician to assess how aggressive the tumor is, to distinguish between a benign or a malignant cancer cell, and to detect the reoccurrence of the tumor depending on the biochemical changes of the cancer cell.

RADIOACTIVE ISOTOPES

PET imaging is conducted with the use of short lived radioactive isotopes. These isotopes are first produced in a machine called cyclotron, and due to the limited half-life of radioisotopes, the cyclotron must be kept in close proximity to the PET scanner prior to examination. Isotopes typically used for PET imaging are carbon-11 (20 min),

Figure 1. PET scanner.

nitrogen-13 (10 min), oxygen-15 (2 min), and fluorine-18 (110 min). The isotopes are then tagged to compounds the body naturally metabolizes like ammonia, water, and glucose. These newly labeled compounds are now referred to as radiotracers. Once prepared, the radiotracer can now be administrated via oral, nasal, or intravenous route. The patient is instructed to fast for 4-6 hours prior to the administration of the radiotracer. Blood glucose level is drawn and monitored at the time of the administration since the radiotracer is glucose analog.

The active molecule is then allowed to circulate and concentrate for 60-90 minutes in tissues that have an increased demand for glucose. The radiotracer will then emit radioactive radiation that is detected by the PET scanner producing an image. Images generated will display areas of focal abnormalities or "hot spots" collecting in tissues cells with increase glucose uptake. Different colors or degrees of brightness on a PET image represent different levels of tissue or organ function. The images are reviewed by a nuclear medicine physician who determines and confirms areas of abnormal uptake based on visual assessment by comparing both asymmetrical and symmetrical views of the area in question.

PHYSIOLOGICAL MECHANISM OF F18- FDG

The most common tracer used is F-18 Flurodeoxyglucose. This glucose analog is typically given in a dosage of 10-15 millicuries (mCi). F-18 FDG is phagocytised by macophages and phagocytic cells via D-glucose-transporter. Through glycolysis, F-18 FDG is phosphorylated by hexokinase resulting in FDG-6 phosphate. Further reaction within the cell is hindered once oxygen is substituted for phosphorylated F-18, since phosphorylated cells are unable to exit the cell due to their increase in ionic charge thus trapping FDG within the cell (Figure 2). An increase in the accumulation of FDG within cells like tumor cells, inflammatory cells and brain cells will in turn amplify the intensity of the radioactivity.

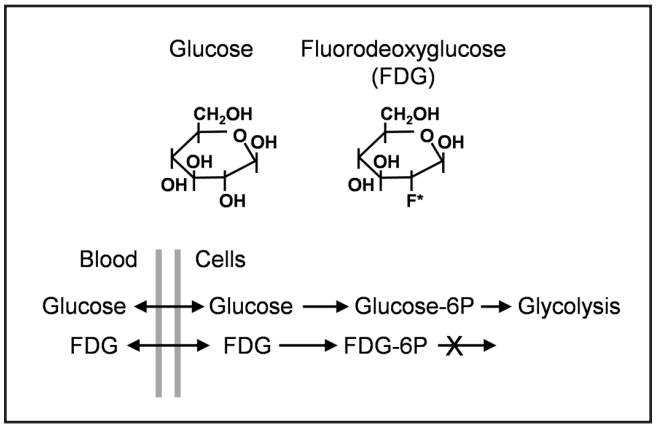

Figure 2. Metabolism of FDG compared with that of glucose.

CLINICAL APPLICATIONS

In clinical cardiology, PET imaging is used to detect and identify pathologic signs of coronary artery disease and atherosclerosis. By uncovering areas of decreased cardiac function and assessing myocardial perfusion, this information can later be used to screen patients who are at risk for developing myocardial infarctions and other vascular disease disorders affecting the heart.

In clinical neurology, PET imaging is used in the detection of chronic conditions like cerebral vascular disorders, epilepsy, Alzheimer's disease, and other disorders like dementia, movement disorders associated with Parkinson disease, mood disorders, and areas of memory loss. Through monitoring cerebral blood flow, metabolic activity as well as cell viability, appropriate measures can be made to determine the correct therapeutic management of the disorder at hand. Currently, the use of PET imaging has demonstrated its efficacy in diagnosing inflammatory and infectious disorders including asthma, tuberculosis, sinusitis, abscesses, cellulites, and chronic osteomyelitis.

DISCUSSION

Chacko et al in 2002 performed a study regarding the application of FDG PET in the diagnosis of an infection by evaluating 56 patients for chronic osteomyelitis. Of the 34 total patients, 31 were diagnosed with osteomyelitis, indicating the ability of FDG PET to detect the presence of chronic osteomyelitis (revealing a sensitivity of 91.2%.) FDG PET was able to exclude 21 of the 23 patients who had noninfected sites indicating a specificity of 91.2%. FDG-PET was also able to detect the presence of bone and soft tissue infection in 27 of 30 patients with a sensitivity of 90.0% and exclude bone involvement with a specificity of 95.0%, thus signifying the overall accuracy of 92.3%.

In earlier reports by Basu et al, osteomyelitis showed intense and well-defined areas of FDG uptake in the bone. The accuracy of FDG PET was also determined in the study by Zhuang et al in 2000, where 16 out of 22 patients were correctly diagnosed with osteomyelitis. However, 2 of the patients recently had osteotomies resulting in inflammatory reactions that lead to false positive results.

FDG PET has proven to be sensitive and specific in the detection of infection. When compared with other

nuclear medicine imaging modalities FDG PET proved to be more accurate and superior in successfully detecting the presence of an infection. For example, bone scans indicate great sensitivity, yet results of the image can be ambiguous because abnormal results can persist even after successful treatment since they work by detecting osteoblastic activity. The use of bone scans like Indium-111 labeled leukocyte and Galium-67 citrate imaging also has its disadvantages showing an increase in the number of false negative results. Both have long preparation processes and low detection rates resulting in poor spatial resolution.

Another concern regarding Indium-111 is the blood handling process, which includes separating, labeling and re-injecting white blood cells into the patient. With such a prolonged and complex process the results may lead to sub-optimal preparation, ultimately increasing the probabilities of introducing an infection between the examiner and patient. FDG PET can provide results within a few hours when compared with Indium-111, or Ga-67 which require imaging 24 to 48 hours after the application of the radiotracer.

MRI is the modality of choice for infection diagnosis, however the presence of metal artifacts in some patients can complicate MRI image results and image interpretations. Residual abrasions can affect image interpretation even once metal devices have been removed. FDG PET images are not affected by such devices, especially when these devices are deemed important in patients who have developed inflammatory reactions. These results suggest that FDG PET can serve a complimentary role when MRI results remain questionable.

PET imaging can be used alone or in conjunction with CT in diagnosing and treating a variety of disorders. The use of PET/ CT together represents the next level in diagnostic modality. PET imaging detects an increase metabolic activity while CT provides anatomic location. The 2 methods combined allow for a more precise anatomic localization of PET abnormalities and in general has been shown to enhance diagnostic accuracy when compared with FDG PET alone (Figure 3).

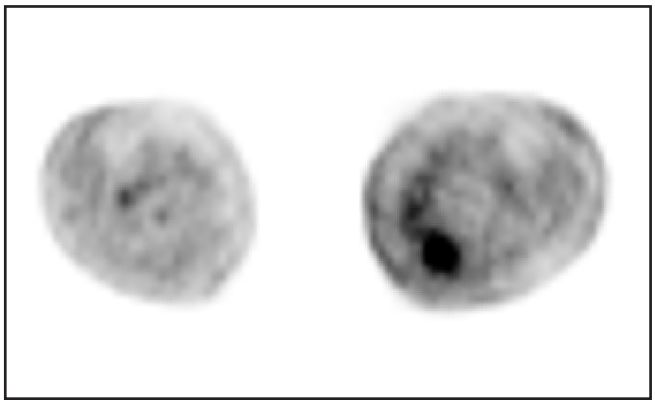

Figure 3. Sagittal view of left lower extremity with deep vein thrombosis.

SUMMARY

When evaluating a patient undergoing an inflammatory process there is still a need to perform a thorough clinical and laboratory examination. Results from patient examination such as blood cultures, leukocyte count, erythrocyte sedimentation rate, and standard radiographs must all be evaluated before a final diagnosis can be made. Overall, FDG PET imaging is an effective imaging adjunct that serves as a diagnostic tool in the detection and assessment of patients with an infection.

Although PET and CT combined provide superior sensitivity and specificity when compared with bone scans, they are still cost prohibitive, because the Food and Drug Administration has not approved PET imaging in the detection of inflammatory and infectious reactions. More research is needed to approve the efficacy of PET imaging in the diagnosis of infections.

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