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PET Radiotracers

RADIOISOTOPES

There are several positron-emitting radioisotopes that have been used for PET imaging. The first four isotopes in Table 1 are of particular note with regard to imaging biological systems. Carbon, nitrogen, and oxygen are key elements for biological systems. Each of them has a pure positron-emitting radioisotope, and none of them has an appropriate single-photon-emitting radioisotope. Fluorine, the fourth entry in the table, is not a normal element in biological systems, but fluorine can often replace either a hydrogen atom or a hyroxyl moiety. It also is a pure positron emitter and does not have a useful single-photon-emitting isotope.

Early in the development of nuclear medicine, the biological significance of these radioisotopes was realized, and positron emitters were viewed with great promise. The availability of these biological radioisotopes has made a major impact on PET research. A vast array of biological radiotracers has been used to help understand kinetics and function. There has been a rich PET literature over nearly half a century.

However, the great promise of these isotopes was not realized in clinical nuclear medicine until recently. The second column in Table 1 may help to explain why. The half-lives of these four isotopes are very short. Oxygen's two-minute half-life means that it needs to be pumped directly from a cyclotron to the scan room. Nitrogen's ten-minute half-life and carbon's twenty-minute half-life are a bit easier to work with, but these half-lives mean that there is little

Table 1: Radioisotopes

Isotope	*Half-life*	β^+ *Energy (MeV)*	γ *Energy (MeV)*
C-11	20.4 m	0.385 (99.8%)	
N-13	9.97 m	0.492 (99.8%)	
O-15	122 s	0.735 (99.9%)	
F-18	110 m	0.250 (100%)	
K-38	7.64 m	1.216 (99.3%)	2.167 (99.8%)
Cu-62	9.74 m	1.315 (97.6%)	
Cu-64	12.7 h	0.278 (17.9%)	
Ga-68	68.1 h	0.836 (8.79%), 0.352 (1.12%)	1.077 (3.0%)
Rb-82	75 s	1.523 (83.3%), 1.157 (10.2%)	0.776 (13.4%)
I-124	4.18 d	0.686 (11.3%), 0.974 (11.3%)	1.691 (10.4%), 7.228(10.0%), 1.509 (3.0%), 1.376 (1.7%), 1.325 (1.43%)

The average energy of the β^+ is given along with the percentage of decays in which the β^+ is emitted. The energy of gamma rays that occur in more than 1% of decays is given along with the percentage of decays in which that gamma ray is emitted.

time for radiopharmaceutical preparation and delivery to the imaging suite. Carbon-11 radiopharmaceuticals that require syntheses that take several half-lives have been used, but long synthesis times rapidly run into practical limits. During the early phase of PET development an on-site cyclotron was typically required.

Even with an on-site cyclotron, these short half-lives limit the biochemical and physiological processes that can be imaged. Single-photon nuclear medicine studies often allow hours or even days for radiopharmaceutical localization. Carbon-11, nitrogen-13, and oxygen-15 can only be used to study processes that have rapid uptake. Fluorine-18 with an approximately two-hour half-life allows more time for synthesis and for imaging somewhat longer physiologic processes.

Decay Schemes. The decay schemes for carbon-11, nitrogen-13, oxygen-15, and fluorine-18 are very simple. Nearly all decays emit a single positron, and there are essentially no photons emitted. The decay schemes for some of the other positron-emitting radioisotopes are more complicated. There may be several transitions that emit positrons of different energies (the most common are listed in Table 1). The progeny nuclei are often produced in an excited state, and several different prompt gamma rays may be emitted.

During the decay of a single iodine-124 atom, both a positron and one or more gamma rays may be emitted. Prompt gamma rays may cause problems with positron cameras. It is possible for one of the gamma rays to be recorded as a photopeak event. If this occurs, then there can be false coincidences between the gamma ray and one of the annihilation photons. Since the directions of the gamma ray and the annihilation photons are not related, these false coincidences will not give valid position information. This interesting problem does not, however, affect the radioisotopes that are the focus of this book.

Radioisotope Production. There are three principal methods that are used for production of radioisotopes in nuclear medicine. Radioisotopes can be produced by separation of the by-product produced during fission; they can be produced from neutron irradiation in a reactor; or they can be produced from bombardment of a target material by charged particles from accelerator.

The low-molecular-weight PET radioisotopes (C-11, N-13, O-15, and F-18) are all produced by charged particle bombardment. Typically, the radioisotopes are produced in a cyclotron, although other charged particle accelerators can be used. The charged particles that are used are usually the nuclei of very low weight isotopes, hydrogen, deuterium, or helium. The hydrogen nucleus is a single proton; the deuterium nucleus is one proton and one neutron; and the helium nucleus is two protons and two neutrons.

These very low molecular weight elements are converted to ions before injection into a cyclotron. Stripping an electron from the atom can produce a positive ion. There has been an increasing use of negative ion sources, where an electron is added to a neutral atom. Although it is somewhat harder to produce negative ions, it turns out that negative ions make it easier to in extract the beam from a cyclotron. Two electrons can be stripped from a negative ion by passing it through a carbon foil producing a positive ion that then turns in a different direction in the magnetic field of the cyclotron, allowing the beam to be extracted.

Nuclear Reactions: When accelerated to high energies, these charged particles can be smashed into nuclei of other elements. The high energy is used to overcome the electrical forces which keep the positively charge nuclei apart. After overcoming these forces, the nucleons can interact using nuclear forces to form new isotopes. Typically, a high-energy particle smashes into an isotope of an element and some other high-energy particle is emitted.

The nuclear reactions are written with the target isotope on the left, the product isotope on the right, and the incoming and outgoing particles separated by a comma within parentheses in the middle. An example, of a typical reaction for producing fluorine-18 is

O-18(p,n)F-18

where p is a proton, and n is a neutron. The high-energy proton interacts with the oxygen-18 nucleus. A high-energy neutron is emitted, leaving a fluorine-18 isotope. Since the incoming and outgoing particles each represent one nucleon, the **mass number** (N) of the product, fluorine-18, is the same as the target, oxygen-18. However, a proton replaces a neutron, thus the **atomic number** (Z) of the isotope increase and the chemical species changes from oxygen to fluorine. Some common reactions are shown in Table 2.

Some of the stable isotopes needed for the targets are easily obtained. Nitrogen-14 represents 99.6% of natural nitrogen. Oxygen-16 represents 99.8% of natural oxygen. The target for these reactions can be made from the naturally occurring element. However, oxygen-18 has a natural abundance of only 0.2%. Thus, the oxygen-18 needs to be separated from the much more common oxygen-16. In the mid-1990s the supply of oxygen-18-enriched water was somewhat tenuous. More recently, there has been a more abundant supply of oxygen-18-enriched water.

Production Yield: The nuclear reaction rate varies depending up the energy of the incoming charged particle. The dependence of this rate on energy is different for each nuclear reaction. Fortunately, there are practical reaction rates for production of all the low-weight positron emitters at relatively low energies. That means that these isotopes can be produced with relatively inexpensive cyclotrons. For example, a "medical" cyclotron which can accelerate protons to 10–15 MeV and deuterons to 5–7.5 MeV can be used to produce C-11, N-13, O-15, and F-18.

The production yield depends on how likely a particle of a certain energy is to react with a particular nucleus. This probability is given in terms of the apparent cross-sectional size of the nucleus. A convenient unit of measurement is the barn, which is 10^{-24} cm^2. The nuclear physicist who created it whimsically named this unit a barn, because is "as big as a barn". It also depends on how many particles there are in the accelerator beam. The number of particles in the beam is given in terms of current, typically in units of microamps.

Table 2: Isotope Production Reactions

N-14(p,α)C-11
O-16(p,α)N-13
N-14(d,n)O-15
O-18(p,n)F-18

Targets: Although cyclotron currents are quite low, the energy of each particle is quite high. Thus, the amount of energy in the beam is quite high. This high energy poses several problems for cyclotron targets. The targets must be able to dissipate the heat from the beam. The beam must pass through a "window" to reach the target material. In order to minimize loss of energy in the window, it is desirable to have a thin window. But the window must also be able to withstand the high energy in the beam.

Various target materials are used. In the case of FDG, the target material is water that has been enriched in the oxygen-18 isotope. Like fluorine-18, nitrogen-13 is also produced from a water target. The nitrogen is scavenged as ammonia by using a small amount of ethanol in the target. Carbon-11 and oxygen-15 are produced from nitrogen gas targets.

FDG Synthesis: Flourine-18 is produced in the target water as HF. The target water usually has a small amount of potassium carbonate, so the F-18 is recovered in the target water as the KF. Tetraacetylmannose triflate is reacted with the fluoride ion and the acetyl protection groups are removed basic hydrolysis. By starting with mannose, the desired optical isomer, D-glucose, is produced.

The FDG synthesis process is automated in a "black box," which can be purchased from the cyclotron manufacturers. Target irradiation, transfer to the "black box," and synthesis of the labeled FDG all takes place under remote control. Automation reduces radiation exposure and improves reproducibility.

RADIOPHARMACEUTICALS FOR CLINICAL PET

From the earliest development of PET scanning in the 1950s until the mid-1990s, PET remained an important research tool. However, because of the complexity of radiopharmaceutical development on-site, the clinical impact of PET was small. FDG (fluorine-18 labeled 2-flouro-2-deoxy-D-glucose) made clinical PET scanning possible. The large number of common clinical indications for FDG means that PET scanning has now reached a critical volume, so that pure clinical PET facilities are reasonable. A moderately sized hospital can support full-time operation of a PET scanner using FDG.

The critical volume of FDG imaging has allowed development of an industry to supply FDG throughout the United States and much of the world. Isotope production, radiopharmaceutical synthesis, and regional delivery of a product with a half-life less than two hours are impressive technological feats. But, these technological hurdles have been overcome, and a supply industry is now in place.

In addition to FDG, rubidium-82 is commercially available. Rubidium-82, a positron-emitting analog of potassium, has a very short half-life, 75 seconds. However, it can be obtained from a strontium-82/rubidium-82 generator as a sterile bolus for injection. The strontium-82 parent has a 25-day half-life. Although the strontium-82 parent is expensive to produce, the cost can be spread over a large number of patients given an active myocardial imaging practice. Commercial services allow sharing a generator between more than one facility.

The infrastructure that has made FDG and rubidium-82 a clinical reality should facilitate the introduction of new radiopharmaceuticals. The isotope production, the delivery system, and the clinical scanners are already in place.

All that needs to be added is new hot chemistry boxes to produce different radiopharmaceuticals. Since the development of radiopharmaceutical will be much easier now that clinical PET is firmly in place, it is reasonable to expect to see an accelerated expansion in the development of new radiopharmaceuticals.

GLUCOSE METABOLISM

Most Cancer Has a High Glucose Metabolic Rate. In the fasting state, most tissues use free fatty acids to supply their energy needs. The brain always uses glucose as a substrate, and many other cells occasionally use glucose. After a meal that includes glucose, insulin rises and several tissues will switch from free fatty acid to glucose metabolism. FDG imaging for malignancy is performed in the fasting state where the uptake by non-malignant tissues is low.

In general, malignant cells tend to use glucose in preference to free fatty acids. Otto Warburg noticed this general principle early in the last century. In addition, if the malignant cells are hypoxic, they will use anaerobic metabolism. Anaerobic metabolism requires much more glucose than aerobic metabolism. Even when malignant cells are not hypoxic, malignant cells tend use anaerobic metabolism. Thus it is common for malignant cells to use glucose and to use a large amount of glucose.

Many cancers are associated with a high metabolic rate. It is common parlance to refer to FDG imaging as metabolic imaging with the implication that tumors are detected because of their higher rate of metabolism than surrounding tissues. This is certainly one mechanism, but in addition FDG imaging takes advantage of reduced background by studying patients during the fasting state and it takes advantage of the frequent use of anaerobic use of glucose by the cancer. More accurately, one should say that FDG imaging reflects glucose metabolic rate.

Tracing Glucose Metabolism. It would seem that radioactive glucose would be the best chemical to use to trace glucose metabolism. Although this seems like the obvious choice, there are problems using radioactive glucose. Most of the glucose that is taken up by cells is promptly metabolized into water and carbon dioxide, both of which rapidly return to the general circulation. Rapid washout makes measuring glucose metabolism difficult under any circumstances; however, it is particularly difficult for imaging.

Sokoloff et al. used 2-deoxy-D-glucose instead of glucose itself to measure glucose metabolism. The missing hydroxyl group in the 2-position had relatively little effect on uptake or phosphorylation, but inhibited the transformation of deoxy-glucose-6-phosphate to deoxy-fructose-6-phosphate, thus preventing further stages in glucose metabolism. Thus, the deoxyglucose accumulated in cells in proportion to its uptake and phosphorylation. Since these steps are rate limiting, the accumulation of deoxyglucose was in proportion to glucose metabolism.

Wolf et al. found that the same mechanism worked when the hydroxyl in the 2-position is replaced by fluorine. 2-fluoro-2-deoxy-D-glucose (FDG) is shown in Figure 1. FDG like deoxyglucose accumulates in cells in proportion to glucose metabolism. With FDG it is possible to take a static image where the relative distribution of FDG will reflect the dynamic metabolic process.

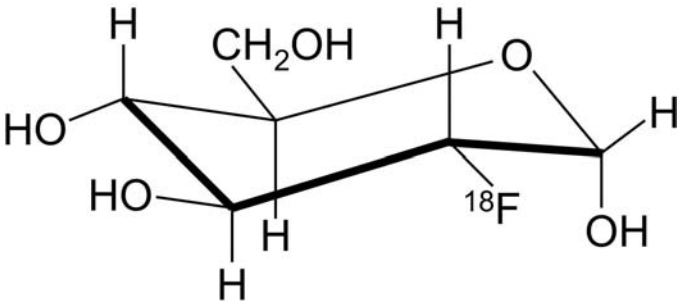


Figure 1: 2-Fluoro-2-Deoxy-D-Glucose. 2-fluoro-2-deoxy-D-glucose (FDG) is an analog of D-glucose where the hydroxyl in the 2 position is replace by fluorine-18.

COMPARTMENTAL MODEL OF FDG UPTAKE

Figure 2 shows a compartmental model of the uptake of FDG. The compartment on the left represents the FDG in the blood. The middle compartment represents the FDG inside a cell. The compartment on the right represents FDG-6-phosphate. Glucose transporters in the cell membrane facilitate the transport of glucose and FDG across the cell membrane. Glucose and FDG are phosphorylated in the 6 position by hexokinase. Phosphorylation reduces the glucose concentration in the cell, so less glucose diffuses back out of the cell than enters the cell.

The conversion of glucose-6-phospate or FDG-6-phosphate back to glucose of FDG respectively, is performed by phosphatase. In most tissues including cancer, there is little phosphatase activity. A notable exception is the liver and some hepatocellular carcinomas. One of the functions of the liver is to maintain the blood glucose level during fasting, and it uses phosphatase to return glucose-6-phosphate to glucose.

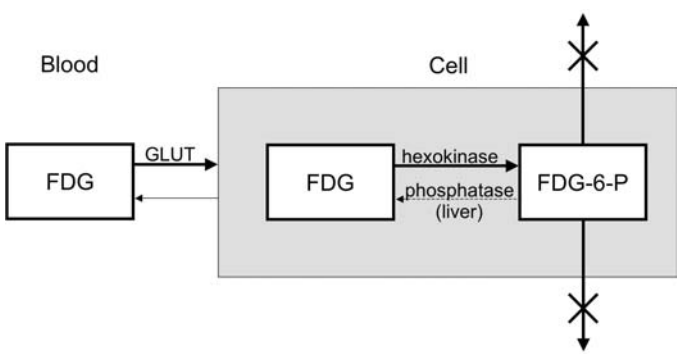


Figure 2: FDG Compartmental Model. Uptake of 2-fluoro-2-deoxy-D-glucose (FDG) from the blood into the cells is facilitated by the glucose transporters (GLUT). Since the blood glucose concentration is typically higher than the intracellular concentration, the inward rate is higher than diffusion out of the cells. Hexokinase converts FDG to FDG-6-phospate (FDG-6-P). Most cells with the notable exception of the liver have little phosphatase. FDG-6-P is not a substrate for further metabolism.

The enzymes that further metabolize glucose-6-phosphate cannot use FDG-6-phosphate as a substrate. Thus, FDG-6-phosphate is not made into glycogen, and it is not metabolized in either the glycolytic or hexose monophosphate paths. Instead the FDG-6-phosphate accumulates in the cell.

Glucose Transporters. There are two families of glucose transporters, the sodium-glucose transporters and the facilitative transporters. The **facilitative glucose transporters** (**GLUT**) are most important for glucose uptake into cells. They transport glucose down a concentration gradient from the blood into the cells. There are at least 12 different glucose transporters. GLUT1 is responsible for transport of glucose into the erythrocytes and across the blood—brain barrier. It is also very important for FDG imaging in oncology, because it is often expressed heavily in malignant cells. Serum insulin levels do not affect GLUT1 expression. By contrast, GLUT4, which is found in muscle, is-up regulated by insulin.

The second family of glucose transporters, the **sodium-glucose transporters** (**SGLT**), co-transport sodium down a concentration gradient and glucose up a concentration gradient. The sodium concentration gradient is maintained by the sodium-potassium ATPase, which ultimately provides the energy for glucose transportation against a gradient. Sodium-glucose transporters are used in the intestine for absorption of glucose and in the kidney for reuptake of glucose from the glomerular filtrate.

Excretion of FDG. Glucose and FDG are freely filtered by the glomerulus. Glucose is then reabsorbed by the nephron. When the serum concentration of glucose is very high, the glucose in the glomerular filtrate can overwhelm the ability of the nephron to reabsorb the glucose and glucose is "spilled" in the urine.

The sodium-glucose transporter in the early portions of the proximal convoluted tubule (SGLT2) co-transports one glucose molecule with one sodium ion. Farther down the proximal convoluted tubule, (SGLT1) co-transports one glucose with two sodium ions. In the initial part of the proximal convoluted tubule, glucose is transported with a lower energy cost; in the later part of the proximal convoluted tubule, the concentration in the urine is reduced at higher energy cost so that almost no glucose escapes into the urine. Within the tubular cells, facilitative glucose transport returns glucose to the plasma.

FDG is a poor substrate for the sodium-glucose co-transporters. Only about half of the FDG undergoes reuptake in the nephron. Much of the FDG is excreted in the urine. In a normal patient there will be intense activity within the urinary system that is normal. It is important not to interpret this normal finding as indicating "spillage" of glucose.

The excretion of FDG is a problem for imaging the urinary system or structures close to the urinary system. However, overall, the excretion of FDG may be beneficial for imaging. Urinary excretion means that the plasma level of FDG decreases more rapidly than radioactive glucose would. This allows earlier imaging than would be feasible with glucose.

Renal excretion of FDG could be added to the compartmental model. However, FDG is removed from the blood by processes other than excretion. It is taken up into other tissues, and it is re-released into the plasma, especially by the liver. Thus, many compartments would be needed to model the blood-time

activity curve. Instead, the blood-time activity curve can be used as the input to the simple three-compartment model shown in Figure 2.

Lumped Constant. FDG metabolism is analogous to the first stages of glucose metabolism. Glucose and FDG are transported into the cells by the glucose transporters, and both are converted to phosphates by hexokinase. However, since they are different molecules, the rate constants for uptake, phosphorylation, dephosphorylation, and diffusion out of the cell are different. From a clinical imaging point of view, these differences are negligible. Physiologists who are interested in the fine details of glucose metabolism cannot ignore these differences. What is generally done when using a compartmental model is that the differences in the kinetic factors between glucose and FDG are lumped together into one constant that is called the lumped constant.

Effect of Plasma Glucose in Oncological Imaging. Plasma glucose competes with FDG for transport into the cells and phosphorylation by hexokinase. The FDG uptake will be inversely related to the plasma glucose concentration. Thus, it is useful to measure the serum glucose concentration at the time of FDG injection. If the serum glucose is high, there may be an increase in false-negative findings for oncological imaging. It is desirable for the serum glucose to be below 140 mg/dL, but diagnostic images can often be obtained with glucose levels up to 200 mg/dL and above.

Standardized uptake value (SUV) measurement will be altered by the serum glucose. The standardized uptake value varies inversely with the serum glucose. One way to adjust for the variability in serum glucose is to multiply the standardized—uptake value by 100 divided by the serum glucose level in mg/dL. Even when this mathematical correction is not used, it is important to take the serum glucose level into account any time the standardized-uptake-value is used.

FDG IMAGING PROTOCOLS

Oncology Protocol. In oncological imaging, the goal is to reduce uptake of FDG in normal cells. General patient instructions for oncological imaging are to fast prior to scanning. Some laboratories recommend fasting for as little as four hours. Most laboratories recommend fasting to at least six hours or longer. If a patient arrives with a high serum glucose level, it is typical to proceed with imaging. It is possible that adequate diagnostic information can be obtained, and otherwise the FDG will decay, the scanner time will not be used, and if rescheduled the patient may again present with a high serum glucose. It is useful to note the glucose value in the report and to note the potential for a false negative study in the report.

Diabetic patients pose a particular problem. It is desirable to have the serum insulin low to minimize the uptake of glucose into normal cells, but it is also desirable to have a low serum glucose level. If a patient has a high glucose level, insulin will lower the glucose and hence increase the uptake in normal cells. Unfortunately, it will also increase uptake in normal cells. What is often done is to schedule diabetic patients for the early afternoon. They are instructed to follow their normal schedule in the morning and then to skip lunch. This simple schedule will work for many diabetic patients.

Cardiology Protocol. In cardiac imaging, the goal generally is to increase cardiac uptake of FDG. The heart can use either glucose or free fatty acids to supply its energy needs. There are two strategies for increasing uptake in cardiac cells: increase the serum insulin level or decrease the free fatty acid level. In non-diabetic patients, the equivalent of a glucose tolerance test can be performed. After fasting, 50 g of glucose is given orally. FDG is injected one hour after the glucose at a time when the insulin is high and the serum glucose has returned to normal.

Unfortunately, many cardiac patients are diabetic. In diabetic patients, exogenous insulin must be administered. The most reliable method is to perform a glucose-clamp. Glucose and insulin are infused simultaneously, and the rate of infusion is adjusted to keep the serum glucose in the normal range while the insulin is at a high level. Because insulin drives potassium into the cells, it is also necessary to infuse potassium during the glucose-clamp procedure. There are also several simplified methods for achieving a high insulin level with a normal glucose.

The heart can be made to switch from free fatty acid to glucose metabolism by lowering the serum free fatty acids. One of insulin's effects is to lower serum free fatty acids, so the methods above also have the effect of lowering free fatty acids. However, free fatty acids can be more effectively lowered using nicotinic acid derivatives. Acipomox, a nicotinic acid derivative, has been used successfully for cardiac imaging particularly in Europe.

Delayed Imaging. In most tissues, the model shown in Figure 2 is adequate for understanding clinical imaging. While there is appreciable activity of FDG in the blood, there is continuing uptake of FDG by the tissues. Once inside the cell, the FDG is promptly converted to FDG-6-phosphate. The FDG-6-phosphate is then trapped in the cell. After a reasonable amount of time for uptake (45 minutes to one hour), there is little change in activity in the tissue. Consequently, washout of FDG uptake is often not considered when choosing an imaging time.

FDG washout is, however, important in a few instances. There is often intense FDG activity in the urinary system at the time of imaging. Because FDG is concentrated in the urine, there will continue to be an important amount of FDG extracted until the blood levels of FDG are very low. Furthermore, even after it is extracted from the blood, it takes time for the FDG to be eliminated from the urinary system. Thus, to get an unobstructed view of the urinary system or of structures that lie near the urinary system, delayed imaging can be used.

In most tissues, there is little phosphatase activity. However, phosphatase activity can be important. The liver has considerable uptake of FDG, even in the fasting state. However, one of the functions of the liver is to supply glucose to the circulation during fasting. Thus, phosphatase is important in the kinetics of FDG in the liver. At the usual time of imaging (about one hour) there is moderate liver uptake. This uptake can mask small or low-uptake FDG-avid lesions. With time there is a decrease in the normal background FDG activity, so that these types of lesions may become more conspicuous.

There tends to be very low washout of FDG from tumor cells. There is evidence that inflammatory tissue, which is a major source of false-positive findings in oncological imaging, may have appreciable washout. Thus, some

investigators have found that comparison of uptake on early (say, one-hour) images with uptake on delayed (say, three-hour) images can help to distinguish inflammation from cancer.

Maximal FDG Activity. In most tissues, FDG continues to accumulate with time. There is a relatively rapid decrease in the blood activity, so the majority of the uptake takes place early, during the first half-hour, with some uptake during the second half-hour. The rate of FDG accumulation decreases considerably after the first hour. Fluorine-18 has a short half-life, 110 minutes. The decay of fluorine-18 competes with the continued uptake of FDG in terms of the total activity of FDG in the tissues. The maximal signal-to-noise given these two considerations often occurs at somewhat less than one hour. For this reason, clinical scan times starting at 45 minutes to one hour are often used.

The previous section noted that the contrast between two tissues may improve with a greater delay time. This improvement also needs to be balanced against the decrease in activity due to decay. Even if the contrast improves, the increased noise may make an FDG-avid lesion less visible.

Instrumentation considerations also need to be considered when selecting an imaging time. Dual-use Anger camera PET scanners have a very low maximum count rate. Consequently, it is common to use a low administered dose of FDG with these machines. An alternate is to use a standard administered dose and image at a more delayed time. The low peak noise-equivalent-count rate of these machines is ameliorated in part by better contrast obtained with delayed scanning.

Dedicated PET scanners with little axial collimation, e.g., "3D" mode, may suffer from a high randoms rate at early scan times. The reduction in randoms rate as the activity decreases will slow the decrease in noise-equivalent-count rate. This effect may also tend to favor somewhat later scan times.

Picking an imaging time is a fairly complex tradeoff that involves several factors. Fast coincidence time, low random rate, high axial collimation, and fixed tissue contrast ratios will tend to favor imaging at earlier times. Slow coincidence time, high randoms rate, little axial collimation, and tissue contrast ratios that increase over time will favor imaging at later times.

ALTERED FDG BIODISTRIBUTION

Muscle Uptake. **Localized Muscle Uptake**: Exercising muscle or muscle post-exercise uses glucose as an energy substrate. Resting muscle predominantly uses free fatty acids. Thus, part of the instructions for patients is to avoid strenuous exercise for at least one day prior to imaging. In addition to intentional exercise, muscles may be used inadvertently. For example, a patient may swing his/her leg or tap his/her finger. Chewing gum can increase uptake in the muscles of mastication. Talking can increase uptake in the vocal chords. In patients with recurrent laryngeal nerve palsy, there is often intense unilateral uptake in the vocal cord region. If a patient is tense, there can be uptake in the neck muscles, torticollis being an extreme example. Latissimus dorsi uptake, either unilateral or bilateral, is seen often. A small dose of a muscle relaxant, e.g., 5–10 mg of diazepam (Valium), can markedly reduce muscle uptake as well as uptake in brown fat (see below).

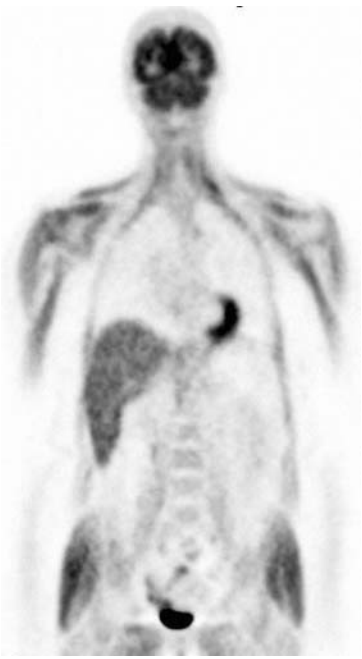
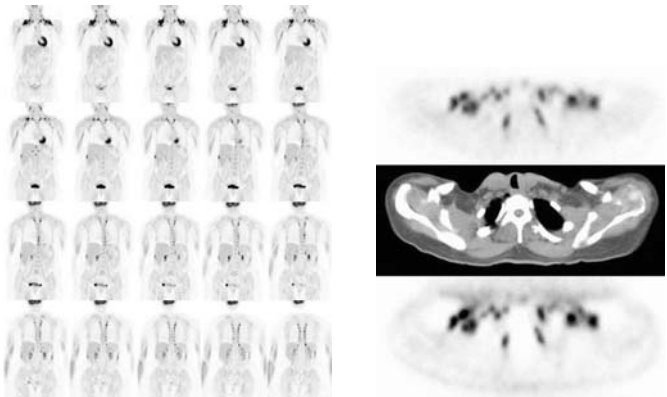


Figure 3: Diffuse Muscle Uptake. This image is a thick coronal section of a patient who reported having a large meal just prior to FDG injection. Note the prominent skeletal muscle uptake due to the postprandial, endogenous insulin release.

Diffuse Muscle Uptake: Diffuse muscle uptake can be seen when there is an elevated serum insulin level (see Figure 3). Insulin translocates the GLUT3 to the surface of the cell, thereby increasing the uptake of FDG.

Myocardial Uptake: Myocardial uptake is quite variable. There is high myocardial uptake in the presence of either high insulin or low free fatty acid in the plasma. Patient preparation to increase the myocardial uptake of FDG is described in the chapter on myocardial imaging. In fasting patients, there may be no uptake in the myocardium; there may be uniform uptake in the myocardium; or there may be non-uniform uptake. The lateral wall most often shows FDG uptake. The septum least often shows uptake. An important point is that a defect in uptake of FDG in a fasting patient should not be interpreted as myocardial disease.

Brown Fat. Brown fat has recently been recognized as an important cause of altered FDG biodistribution. Brown fat is involved in thermoregulation prior to the point of shivering. It is found abundantly in rodents. It used to be thought that brown fat did not occur in the adult human, but recently it has been found that brown fat can be seen in adults. Brown fat is often found in the neck, along the spine, and occasionally in the abdomen (see Figure 4). Brown fat is richly supplied with vessels and with sympathetic nerves. Patients who are nervous or



A B

Figure 4: Brown Fat Uptake. Coronal FDG-PET images in a patient with brown fat uptake are shown in part A. Note the typical spotty appearance in the neck and the paravertebral uptake. This patient also has some uptake in brown fat in the abdomen. Part B shows registered attenuation corrected FDG, CT, and uncorrected FDG slices which show the location of the uptake corresponds to fat on the CT.

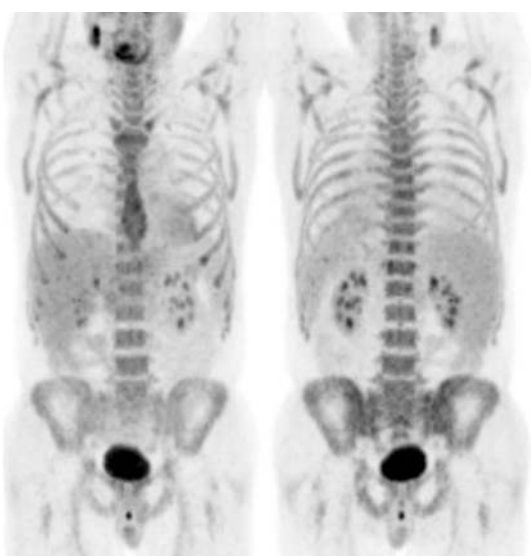


Figure 5: Diffuse Bone Marrow Uptake. Anterior (left) and posterior (right) maximum intensity renderings show diffuse bone marrow uptake in a patient treated with bone marrow stimulants.

cold may show spotty uptake in the neck and along the spine due to the brown fat.

Brown fat can be confused with neck muscle uptake, although neck muscle uptake is more linear and brown fat uptake is more spotty in distribution. Originally, brown fat uptake was confused with muscle uptake. Brown fat uptake can also be abolished by low does of diazepam (Valium). And this response to muscle relaxants reinforced this confusion. However, with the introduction of PET/CT, it became apparent that the spotty type of uptake was located in fat not muscle. In children, uptake of meta-iodo-benzyl-guanidine (MIBG) and tetrofosmin in brown fat has also been recognized.

Bone Marrow. There is normally uptake in the bone marrow on FDG. The uptake may be intense in patients treated with stimulating factors or in patients rebounding from chemotherapy (see Figure 5).

Areola. The uptake in the areola is variable, but prominent uptake may be seen (see Figure 6).

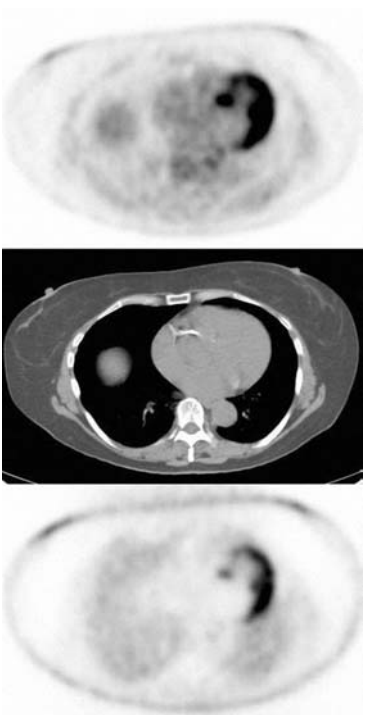


Figure 6: Areolar Uptake. This patient has mild increase uptake in the areolar area. Top is the attenuation corrected FDG; middle is the CT; and bottom is non-corrected FDG.

Thyroid. Uptake of FDG in the thyroid is a relatively frequent variant. Homogeneous intense uptake can be seen in Graves' disease and in subacute thyroiditis. Diffuse uptake is also seen in patients with Hashimoto's thyroiditis. In patients without the clinical diagnosis of Hashimoto's thyroiditis, diffuse uptake is often associated with elevated antithyroid antibody levels. Focal uptake can be seen in thyroid nodules, and increases the chance that thyroid nodules are malignant. Focal thyroid uptake can be further evaluated with fine needle aspiration.

Thymus. The thymus gland may take up FDG in children and young adults. After chemotherapy there can be an increase in the size of the thymus with intense uptake of FDG. This benign finding is called thymic rebound.

GI Tract. There is variable uptake of FDG in the GI tract. It is common to see uptake at the gastroesophageal junction. Diffuse or segmental uptake is often seen in the stomach or the colon. Generally, this uptake is incidental, although some pathological conditions such as lymphoma can cause diffuse or segmental uptake. Focal, intense (greater than the liver) uptake in the colon can be incidental, but it is associated with colon cancer or adenomatous polyps about one-half of the time. Focal colonic uptake can be further evaluated with colonoscopy

Sarcoidosis. There is variable uptake in sarcoidosis, but the uptake can be intense. The pattern of uptake may suggest sarcoidosis, but the patterns of uptake overlap with lymphoma.

Inflammation. Inflammatory cells, particularly macrophages, utilize glucose metabolism. This fact is the basis of imaging infection. In addition,

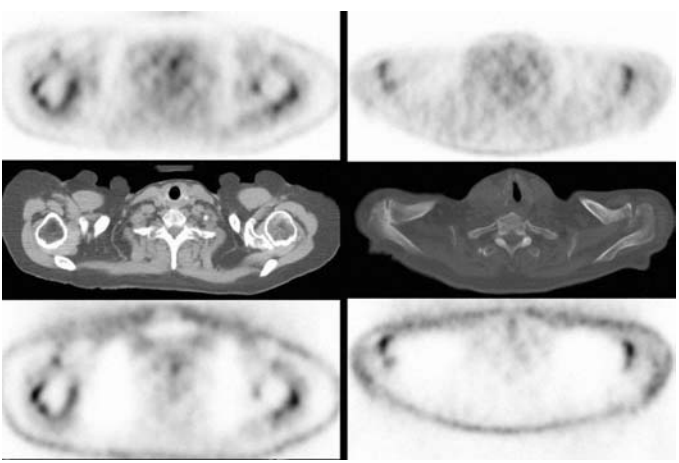


Figure 7: Periarticular Inflammation. The patient shown on the left shows increased uptake around the humeral heads. The patient shown on the right shows uptake at the acromioclavicular joint. Top is the attenuation corrected FDG; middle is the CT; and bottom is the non-corrected FDG.

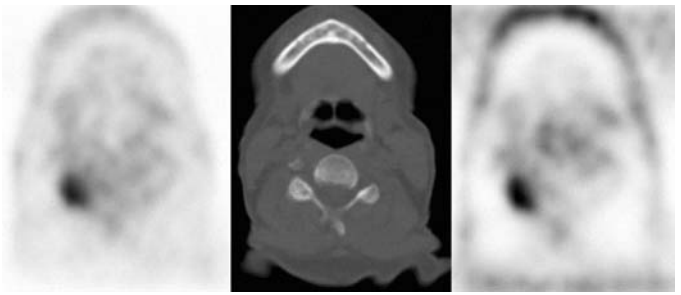


Figure 8: Facet Joint Inflammation. There is intense uptake at the location of facet joint inflammation. Left is the attenuation corrected FDG; in the center is the CT; and on the right is the non-corrected FDG.

inflammatory/infectious conditions can lead to false-positive diagnoses. Reactive lymph nodes, particularly those draining the limbs, frequently show a mild increase in uptake, and occasionally show intense uptake.

Periarticular Inflammation: It is common to see increased uptake of FDG around joints, particularly in association with periarticular inflammation. Close anatomic localization can be useful in distinguishing facet joint inflammatory disease from bone marrow metastatic disease (see Figures 7 and 8).

Granulomatous Disease: Granulomatous lesions particularly fungal disease can cause intense FDG uptake. Fugal granulomatous lesions are a particular problem in the lung. They are a frequent cause of false-positive single pulmonary nodule in regions that have endemic fungal disease.

Silicon: Silicon can cause an inflammatory reaction. It can be a cause of false-positive lymph node uptake. Figure 9 shows an FDG-PET/CT in a patient 12 years post-mastectomy for breast cancer and one year post-saline implant

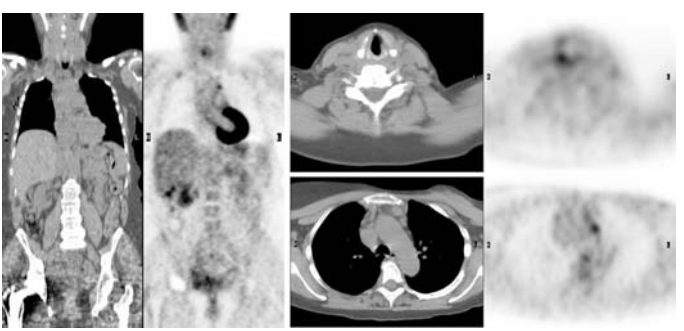


Figure 9: Inflammatory Node Secondary to Silicon. On the left are CT and FDG coronal images, which show focal uptake in the left mediastinum and in the right vocal chord. Also note the right hip prosthesis. On the upper right, CT and FDG axial images through the vocal chord region show uptake on the right. On the lower right, CT and FDG axial images through the chest show uptake in a prevascular lymph node. The larger more anterior lymph node is not FDG-avid.

replacement of a ruptured silicone breast implant. She presented with hoarseness and was found to have left recurrent nerve palsy. The FDG uptake in the region of the right vocal chord is secondary to increased work of the muscles on the right side in compensation for the paralysis on the left side. The moderate uptake in the prevascular lymph node was found on biopsy to correspond to inflammatory reaction compatible with silicone.

MYOCARDIAL PERFUSION AGENTS

First Pass Extraction. There are three conditions that are sufficient for a tracer to be distributed in tissue in accordance with blood flow. 1) The tracer must be mixed across the cross section of blood flow. Streaming of a tracer in the blood after intraarterial injection violates this condition. Agents that are injected intravenously are generally well mixed by the time they get to the pulmonary circuit. 2) The tracer must be completely extracted by the tissue. Particles such as microspheres are the prototype of an agent that is completely extracted in one pass. 3) The tracer must have a stable distribution over the time on sampling. Thallium-201 is an example of a tracer where the washout can be important over the time of imaging.

It is possible to relax the second condition from complete extraction to uniform extraction. The advantage of complete extraction is that it is easy to confirm that all tissues have equal extraction. However, as long as the tracer has the same fractional extraction in all of the tissues of interest, then the distribution will still be according to blood flow. It may take several passes through the tissue to extract all of the tracer, but as long as the same fraction is extracted in each pass, the final distribution will be according to blood flow.

Rubidium-82. **Potassium Analogs:** Rubidium is in the position just below potassium on the periodic table. Both are monovalent cations. The radii are similar enough that both are good substrates for the sodium-potassium ATPase in the cell membrane. Cesium, the element below rubidium, is a less good substrate for the sodium-potassium ATPase. (Although thallium-201 is in a much different location on the periodic table, it is also a monovalent cation with high affinity for the sodium-potassium ATPase.)

There is a marked concentration gradient between the intra- and extracellular fluid for potassium and its analogs. The ATP-dependent sodium potassium pump maintains the gradient. All viable cells are able to maintain the gradients for sodium and potassium. In theory, dead cells would have reduced fractional extraction of rubidium. In practice it is unusual for there to be blood flow to areas where there are no viable cells.

Potassium and its analogs are taken up efficiently after a single pass through tissue. In the myocardium, the first pass extraction of the potassium analogs is about 85%. Furthermore, the extraction of the potassium analogs is fairly uniform in the myocardium. At very high flow rates, particularly after pharmacological vasodilation, there is a small decrease in fractional extraction. At very low flow rates, there is a small increase in fractional extraction. However, in general, the potassium analogs follow the requirement for uniform extraction.

Because of the transmembrane gradient, most of the potassium is within the cell. Relatively little potassium is in the blood or extracellular fluid.

Consequently, the rate of washout of potassium from tissue is relatively slow. From the point of view of the potassium space, the cell is a very large volume, and the blood flow is very low. In terms of potassium space, the blood is a trickle going by a large cell.

In terms of washout rate, it is necessary to distinguish between the one-way washout and the net washout. The one-way washout is what happens to a tracer that starts within the cell. The net washout includes both the washout from within the cell and the wash-in from the blood. Although there is little potassium in the blood, the continued wash-in over long times cannot be ignored. The one-way washout of potassium in man probably has a half-life somewhat over an hour. The net washout half-life is on the order of 6–8 hours.

The very short half-life of rubidium-82 means that washout is never a consideration in its distribution. (This is not true for longer-lived isotopes such as thallium-201.) Thus, rubidium also meets the blood flow tracer requirement for no washout.

Strontium-82/Rubidium-82 Generator: Rubidium-82 has a very short half-life, 75 s. Fortunately, rubidium-82 has a parent, strontium-82, from which a convenient generator system can be produced. Strontium-82 has a half-life of 25.36 days and decays by electron capture to the ground state of rubidium-82. (The energy difference between the strontium-82 and rubidium-82 ground states is too low for positron emission.) Rubidium-82 decays 96% of the time by positron emission, and 4% of the time by electron capture. There are several different beta energies, but the most abundant has an energy of 1.523 MeV. This high energy means that the beta particle may travel far enough in tissue to result in some loss in resolution. In addition to the 511 keV annihilation photons, rubidium-82 decay results in several prompt gamma rays. The most common, 13.4% of decays, is a 776 keV gamma ray. Rubidum-82 decays to krypton-82, which is stable.

Strontium-82 is usually produced in an accelerator by a spallation reaction using high-energy proton bombardment of rubidium-85, Rb-85(p,4n)Sr-82. This (p,4n) reaction requires at least 60 MeV, and it is commercially produced using protons of about 500 MeV. (A **spallation reaction** is where many nucleons are ejected from a nucleus by bombardment with a single very-high-energy incident particle.) Most of the other isotopes produced during bombardment can be efficiently separated; however, some strontium-85, which can't be chemically separated from strontium-82, will also be produced (see radionuclide purity below). Because this reaction requires a high-energy incident proton, the cost of the strontium-82 parent is high. Fortunately, the generator can be used repeatedly and the cost can be distributed over a large number of patients, making use of the generator system feasible.

The strontium-82/rubidium-82 generator is made from hydrous stannic oxide. It is eluted with 50 mL of normal saline over one minute. The generators are usually loaded with 3.33–5.55 GBq (90–150) mCi of strontium-82. A typical dose is 1.5 GBq (40 mCi) with a range of 0.37–2.22 GBq (10–60 mCi).

Ammonia. Nitrogen-13-labeled ammonia is another agent that is approved for myocardial perfusion. Although ammonium, NH_4 , is a monovalent cation with about the same ionic radius as potassium, ammonia uptake is by a different mechanism. Ammonia, NH_3, is highly lipid soluble and can cross the cell membrane easily. Ammonia and ammonium are in equilibrium in the blood

with ammonium being the predominant species. Although ammonium is the predominant species, the equilibrium is fast enough that the transfer into the cell is rapid. Once in the cell, ammonia rapidly undergoes ammonia fixation. This whole process—the equilibrium between ammonia and ammonium, diffusion across the membrane, and ammonia fixation within the cell—is fast enough that ammonia has a high first-pass extraction.

Nitrogen-13 has a short half-life, 10 min, and there is no generator system; therefore, N-13-labeled ammonia is only available in facilities with an on-site cyclotron. The N-13 can be produced using the O-16(p,α)N-13 reaction.

OTHER PET AGENTS

Tumor Proliferation. **C-11-Thymidine**: One hallmark of cancer is rapid cell proliferation. Several positron-emitting radiopharmaceuticals which are correlated with tumor proliferation have been developed. One of the most extensively studied has been C-11-thymidine. Thymidine is a nucleoside that is incorporated into DNA, especially during the synthetic (S) phase of the cell cycle. However, the short half-life of carbon-11 is not well suited to the relatively slow incorporation of thymidine into DNA. The necessity of an on-site cyclotron and radiopharmaceutical synthesis will restrict the use of this agent to academic PET centers.

F-18-FLT: 3′-deoxy-3′-fluorothymidine (FLT) is a thymidine analog with fluorine substituted for the hydroxyl in the 3′ position (see Figure 10). The uptake of FLT has considerable analogy with the uptake of FDG. The phosphorylation of FLT by thymidine kinase 1 is not affected by the presence of the fluorine substitution. The subsequent step in DNA synthesis is, however, prevented by this substitution. Thus, FLT is trapped in the cell. The thymidine kinase 1 activity is a measure of DNA synthesis and hence of cell proliferation.

Buck et al. investigated 26 patients with lung nodules using both FDG and FLT PET. They compared the SUV values in the lesion with a histological marker of proliferation, Ki-67 immunostaining of the specimen obtained at surgery. They found a better correlation between the proliferative activity and the

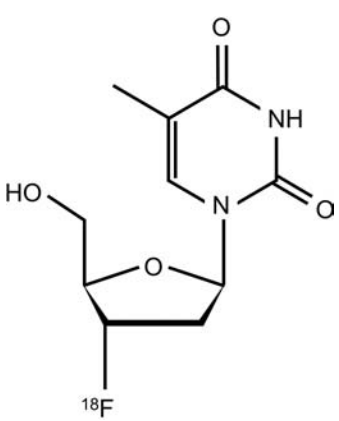


Figure 10: 3′-Deoxy-3′Fluorothymidine (FLT). The chemical structure of FLT is shown.

uptake of FLT (r = 0.92) than the uptake of FDG (r = 0.59). The average uptake of FDG (4.1) was, however, greater with FDG than FLT.

This study is very interesting. FDG uptake reflects glucose metabolism; FLT reflects thymidine metabolism, which reflects DNA synthesis. This study shows that these two different markers are able to reflect different aspects of these pulmonary nodules.

Metabolism. The major PET metabolic tracer is FDG. As already described in some detail FDG reflects glucose metabolism. It is also the only commercially available PET tracer of metabolism. However, there are several other metabolic tracers that have been used and may become commerciallyavailable in the future.

C-11-Acetate: C-11-acetate is a very interesting tracer of metabolism since it reflects the activity of the tricarboxylic acid cycle. Glucose and free fatty acids, which are the major sources of energy for cells, undergo oxidative metabolism in the tricarboxylic acid cycle. C-11-acetate gives a measure of the overall oxidative metabolism. Acetate is rapidly converted into carbon dioxide and water. Therefore, it is necessary to perform dynamic imaging and model the metabolic process.

C-11-Fatty Acids: C-11-labeled free fatty acids, such as C-11-palmitate, can be used to measure fatty acid metabolism. Because of metabolism, the C-11-palmitate information must also be collected with dynamic imaging and be analyzed with a compartmental model.

C-11-Methoionine: C-11-methionine can be used as a measure of protein synthesis.

Blood Flow. Rubidium-82 from a strontium-82/rubidium-82 generator is the only commercially available PET radiopharmaceutical for measurement of blood flow. Nitrogen-13-labeled ammonia can be made in an on-site cyclotron and myocardial perfusion studies using this agent are reimbursable. In addition, many other PET tracers have been used for blood flow measurement.

Pre-capillary Arteriolar Blockade: Relative blood flow can be measured using small particles analogously to single-photon lung scintigraphy. A wide range of positron-emitting isotopes can be labeled to microspheres, to be used for measuring relative blood flow.

First-Pass Extraction: In addition to rubidium-82 and nitrogen-13 ammonia, there are several PET radiopharmaceuticals that can be used to measure relative blood flow using first-pass extraction. Copper-62-labeled pyruvaldehyde bis(N-methylthiosemicarbazone (PTSM), is rapidly taken up inside cells and then trapped by being metabolically altered.

The requirements to be distributed according to blood flow–mixing in the blood flow, uniform extraction in the tissue, and stable distribution–are met at least partially by many radiopharmaceuticals.

When trying to measure another physiologic paramater, say, receptor distribution, first-pass extraction according to blood flow can present a problem. A tracer that has a high affinity for a receptor is often highly extracted and stable in distribution. Thus, instead of measuring the receptor density, the tracer ends up largely reflecting blood flow.

Washout: Absolute blood flow can be measured from the rate of washout of a diffusible tracer from a tissue. After bolus injection the rate of washout

depends on the partition of the tracer between the blood and tissue, and on the blood flow per volume of tissue. In more complicated systems, a compartment model can be used to model the uptake and washout. Often blood flow is one of the parameters that is derived by fitting the data to the compartmental model.

Water is generally freely diffusible in tissue. (Butanol may be more diffusible in the brain.) Water is one of the products of C-11-acetate metabolism. It is also readily available from O-18-labeled carbon dioxide. Carbonic anhydrase catalyses the conversion of carbon dioxide and water to the bicarbonate ion:

$$CO_2 + H_2O \leftrightarrow HCO_3^- + H^+$$

In blood, this reaction proceeds rapidly. The bicarbonate ion is a tetrahedral molecule, where all of the oxygen atoms are equivalent. Thus, a radioactive oxygen element on the bicarbonate will be distributed to the carbon dioxide or water molecule irrespective of which molecule it originated from. With the rapid conversion back and forth between these species, a labeled oxygen molecule will tend to be distributed between carbon dioxide, water, and bicarbonate in proportion to the amount of each species. Since the water pool is many orders of magnitude larger than the carbon dioxide or bicarbonate pools, almost all of the labeled oxygen will rapidly be transferred to the water. In the biological context, it is common PET slang to refer to O-18-labeled carbon dioxide as O-18 water.

RADIOPHARMACEUTICAL PROPERTIES

Radioactivity. Radioactivity is given in terms of becquerels, Bq, where one Bq is equal to one disintegration per second. The unit is named after Henri Becquerel. Typical units used in nuclear medicine are megabecquerels, MBq, or gigabecquerels, GBq, where a megabequerel, MBq, is a million (10^6) becquerels, and a gigabecquerels is a billion (a US billion equal to a thousand million, 10^9) becquerels. In the United States, radioactivity is still given in terms of the older unit, the Curie, Ci, where one Ci is equal to 3.7×10^{10} disintegrations per second. The Curie is named after Pierre Curie. Pierre and Marie Curie shared the Nobel Prize in Physics with Henri Becquerel in 1903 for the discovery of radioactivity. Typical units used in nuclear medicine are microcuries, μCi, or millicuries, mCi, where a microcurie is one-millionth (10^{-6}) of a curie, and a millicurie is one-thousandth (10^{-3}) of a curie. Conversion between units in Becquerels and units in curies can be derived from these definitions, but a convenient conversion for the activities typically used is

$$37 \text{ MBq} = 1 \text{ mCi}$$

Note that the units of radioactivity are given in terms of disintegrations per second. "Disintegrations" refers to the number of atomic nuclei that undergo decay. It does not refer directly to the number of particles or photons that are emitted. The details of the decay process are not important in calculating the radioactivity. For example, flourine-18 almost always emits a positron when it decays, and each positron gives rise to two 511-keV annihilation photons. If one fluorine-18 atom decays each second there are nearly two 511-keV photons

produced per second. Even though there are almost two photons per second, the radioactivity is equal to 1 Bq because that is the number of atoms that are decaying.

Specific Activity. Specific activity is equal to the activity per unit of material. Often it is given in terms of the activity per gram or moles of tracer. The first step is to calculate the number of atoms in a sample from the activity. All of the atoms eventually decay, so the number of atoms is equal to the area under the time activity curve (see Chapter 1, Figure 2). The area under the time activity curve is:

$$N = A_0 \cdot T_{1/2}/\ln(2)$$

where N is the number of atoms. Dividing by Avogadro's number gives the moles. For 370 MBq (10 mCi) of fluorine-18, this number is $370 \cdot 10^6 \cdot 110 \cdot 60/0.693/6.02 \cdot 10^{23} = 5.85 \cdot 10^{-12}$, where $370 \cdot 10^6$ is A_0 in disintegrations/second, 110 is the fluorine-18 half-life, 60 is the number of seconds per minute, 0.693 is ln(2), and $6.02 \cdot 10^{23}$ is Avogadro's number. Note that 370 MBq (10 mCi) of fluorine-18 is an incredibly small amount of fluorine, 5.85 pmole.

FDG, which has a composition given by $FC_6H_{11}O_5$, has a weight of $18 + 6 \cdot 12 + 11 \cdot 1 + 5 \cdot 16 = 181$ g/mole. Multiplying the number of moles by this number gives $1059 \cdot 10^{-12}$ g. Therefore, 370 MBq (10 mCi) of FDG represents about $1.05 \cdot 10^{-9}$ ng of FDG. A typical dose of FDG corresponds to about a nanogram of radioactive material. The specific activity is given as the ratio of the activity to the number of moles or the number of grams of material. In the case of FDG these numbers are 63.3 MBq/pmole (1.71 mCi/pmole) and 349 MBq/ng (9.44 mCi/ng).

These calculations are fairly straightforward, but the number of steps required makes them difficult to perform. There is an ImageJ (http://rsb.info.nih.gov/ij/) plugin (htpp://www.med.Harvard.edu/JPNM/ij/plugins/AtoNTP.html) which does these calculations automatically.

This calculation assumes that all of the FDG is radioactive, that there is no stable FDG. If there is stable FDG, then there will be more grams of chemical FDG for the same amount of radioactive FDG. The specific activity of the FDG will be lower than the specific activity that is calculated above. Fluorine-18-labeled FDG is produced without any bulk excess of FDG, but as is often true with tracer chemistry, there may be some non-radioactive fluorine available. Consequently, the actual specific activities are lower than this completely carrier-free calculation. However, the total chemical quantity of FDG is insignificant from a clinical point of view.

Purity. **Radionuclide Purity**: Radionuclide purity is defined as the fraction of radioactive species that is the desired isotope. Radionuclide purity is usually most important because of radiation dose. If the radiopharmaceutical is contaminated with an unwanted isotope, this isotope will deliver some radiation absorbed dose to the patient without providing any useful information. Radionuclide purity will vary with time after production depending on the half-lives of the desired and contaminant isotopes. If the contaminant isotope has a long half-life, then with time the fraction of the unwanted isotope will increase.

For several PET radioisotopes, there is relatively little problem with radionuclide purity. For example, fluorine-18 is generally produced with very

little contamination by other isotopes. Contamination is more of a problem with the strontium-82/rubidium-82 generator. The high-energy spallation reaction used to produce strontium-82 can result in production of other isotopes as well. Often other isotopes can be separated chemically with high efficiency. However, in the case of strontium-82, one of the other products is strontium-85.

Generator systems usually allow for high-efficiency elution of the progeny isotope with high retention of the parent. Breakthrough of strontium-82 and strontium-85 should be tested for when using a strontium-82/rubidium-82 generator. The rubidium-82 can be measured shortly after elution of the generator. Because of rubidium-82's very short half-life, a correction needs to be made for decay between the time of elution and the time of measurement. The sample can then be allowed to decay until the rubidium-82 is completely decayed. One hour is a convenient time. Then the sample can be measured again. The strontium-85/strontium-82 ratio is provided with the generator. Since strontium-85's half-life, 64.8 days, is longer than strontium-82's half-life, 25 days, this ratio needs to be adjusted using the time since analysis.

Radiochemical Purity: Radiochemical purity is defined as the fraction of the radioactive species that isin the desired chemical form. During synthesis of the radiopharmaceutical, other radioactive species may be produced. After production, the desired radiochemical can be changed to another radiochemical. The special consideration for radiopharmaceuticals is radiolysis. The radiopharmaceutical is often contained in a very small volume. A good deal of energy is deposited in this volume by radioactive decay, often with the production of free radicals. This environment often has deleterious affects on the radiopharmaceutical itself. Fortunately FDG is a very stable compound and undergoes relatively little breakdown after production. However, radiochemical purity, especially when there is an extended time between production and use, can be a problem with other PET radiopharmaceuticals.

CONCLUSIONS

The utility of FDG imaging for a vast number of tumors has made the long-recognized potential of PET a clinical reality. An infrastructure has developed, including a radiopharmaceutical supply network and widely available dedicated PET cameras. Other applications are emerging, e.g., inflammation/infection imaging, neurological imaging, and cardiac imaging. Now that this infrastructure has been developed, it is possible that many other lower-volume studies will flow from development of new PET radiopharmaceuticals, resulting in a flourishing of PET imaging in the near term.

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