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Paans, AMJ. (1999). Positron emission tomography. Acta Physica Polonica B, 30(5), 1619-1628.

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POSITRON EMISSION TOMOGRAPHY*

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(Received August 5, 1998)

Positron Emission Tomography (PET) is a method for determining biochemical and physiological processes *in vivo* in a quantitative way by using radiopharmaceuticals labelled with positron emitting radionuclides as ^{11}C, ^{13}N, ^{15}O and ^{18}F and by measuring the annihilation radiation using a coincidence technique. This includes also the measurement of the pharmacokinetics of labelled drugs and the measurement of the effects of drugs on metabolism. Also deviations of normal metabolism can be measured and insight in biological processes responsible for diseases can be obtained.

PACS numbers: 87.59.Vb

1. General overview

The idea of in vivo measurement of biological and/or biochemical processes was already envisaged in the 1930's when the first artificially produced radionuclides, which decay under emission of externally detectable radiation, of the biological important elements carbon, nitrogen and oxygen were discovered with help of the then recently developed cyclotron. These radionuclides decay by pure positron emission and the annihilation of positron and electron results in two 511 keV γ-quanta under a relative angle of 180° which are then measured in coincidence. This idea of PET could only be realized when the inorganic scintillation detectors for the detection of γ-radiation, the electronics for coincidence measurements and the computer capacity for image reconstruction became available. For this reason Positron Emission Tomography is a rather recent development in functional in vivo imaging.

PET employs mainly short lived positron emitting radiopharmaceuticals. The radionuclides employed most widely are: ^{11}C ($T_{1/2}$ = 20 min),

* Presented at the International Conference "Nuclear Physics Close to the Barrier", Warszawa, Poland, June 30–July 4, 1998.

^{13}N ($T_{1/2}$ = 10 min), ^{15}O ($T_{1/2}$ = 2 min) and ^{18}F ($T_{1/2}$ = 110 min). Carbon, oxygen, nitrogen and hydrogen are the elements of life and the building stones of nearly every molecule of biological importance. However, hydrogen has no radioactive isotope decaying with emission of radiation which can be detected outside the human body. For this reason a fluorine isotope is often used as a replacement for a hydrogen atom in a molecule. Due to these short half lives the radionuclides have to be produced in house, preferably with a small, dedicated cyclotron. Since the chemical form of the produced radionuclides can only be simple, input from organic and radiochemistry is essential for synthesis of the desired complex molecule [1]. Input from pharmacy is required for the final formulation and pharmacokinetic studies and medical input is evident and required for application. Longer lived positron emitting radionuclides are sometimes commercially available or obtainable from research facilities with larger accelerators. Some examples of longer liver positron emitting radionuclides are ^{52}Fe ($T_{1/2}$ = 8.3 h), ^{55}Co ($T_{1/2}$ = 17.5 h) and ^{124}I ($T_{1/2}$ = 4.2 d). Sometimes also positron emitting radionuclides can be obtained from a generator system. Examples are ^{82}Rb ($T_{1/2}$ = 76 s) from ^{82}Sr ($T_{1/2}$ = 25.5 d) and ^{68}Ga ($T_{1/2}$ = 68 m) from ^{68}Ge ($T_{1/2}$ = 288 d). Although all these radionuclides are used, the isotopes of the biological most important elements receive most attention.

At the moment small dedicated cyclotrons are a commercially available product. These accelerators are one or two particle machines with fixed energies. At the moment mostly negative-ion machine are being installed because of their relative simple extraction system and high extraction efficiency. They are installed complete with the targetry for making the four above mentioned short lived radionuclides in Curie amounts. Also the chemistry for some simple chemical products is incorporated *e.g.* $^{11}CO_2$, ^{11}CO, $C^{15}O$, $C^{15}O_2$, $H_2{}^{15}O$ *etc.* Sometimes more complex syntheses, *e.g.* ^{18}FDG (fluorodeoxyglucose), $H^{11}CN$, $^{11}CH_4$ or $^{13}NH_3$, are also available from the cyclotron manufacturer. These products become available via dedicated, automated systems or via a programmable robotic system. Other radiopharmaceuticals have to be set up individually in each PET center.

The state of the art positron camera is a complex radiation detection technology product combined with a relative large computing power for data acquisition and image reconstruction [2]. The basic detector in a modern PET camera is a BGO detector block divided in 8×8 subdetectors read out by 4 photomultiplier tubes (PMT). By adding and subtracting the individual signals of the PMT's the scintillating subdetector in the BGO block can be identified. Around 70 blocks will form a ring and 4 of these rings can be added to get an axial field of view of approximately 15–16 cm. In this way 63 planes are imaged simultaneously with a spatial resolution of 4–5 mm FWHM. The septa between the adjacent subdetector rings can also

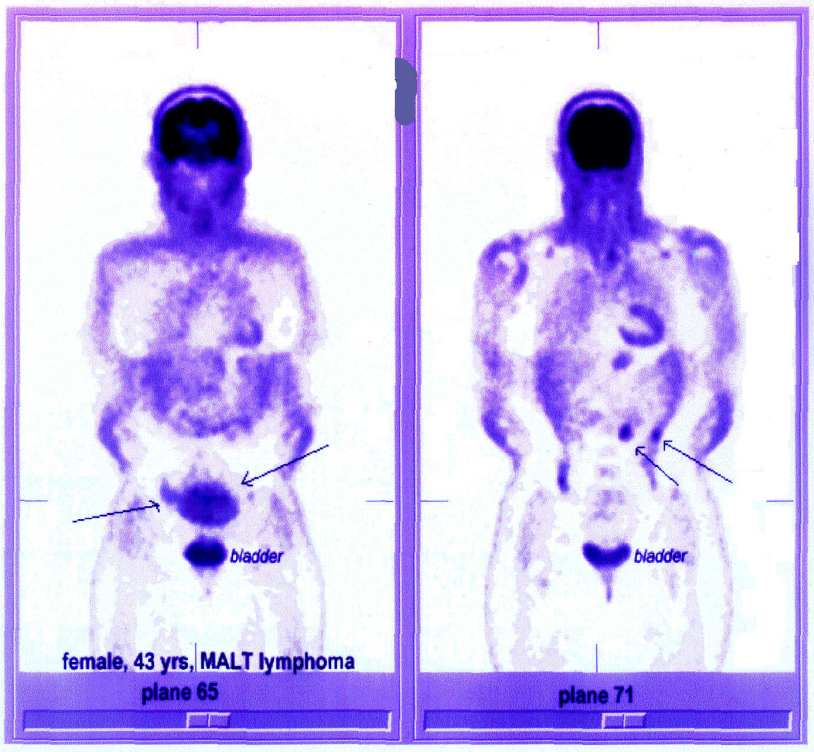

Fig. 1. Whole-body PET-scan with FDG shown at two levels

be retracted creating a much higher sensitivity in this 3-D mode at the cost of a larger scatter fraction. With the present generation of positron camera's the singles count rates that can be managed are in the order of over 50,000,000 counts per second resulting in coincidence count rates of over 500,000 per second. Hardware and software for data acquisition, image reconstruction and for image manipulation is available. Positron cameras are able to measure the radioactivity in absolute terms, Bq/pixel, which is an unique feature. This is possible because the coincidence technique allows for the correction of the attenuation of radiation inside the body of the individual patient. This correction is accomplished by making an individual "transmission image" with an external positron emitting source. This individual transmission image can also be used to correct for scattered radiation present in the image after a 3D-acquisition. This external source is built into the camera and can be extended from its well shielded storage box during the operation of the positron camera. To translate the measured radioactivity distribution into functional or physiological parameters compartimental models have been developed for radiopharmaceuticals with

known metabolite profiles. Although only a few measurable quantities, *i.e.* tissue and plasma concentration (the latter by taking blood samples), are available, it is still possible to calculate *e.g.* the glucose consumption by employing a dynamic data acquisition protocol in combination with a compartimental model [3]. It is also possible to make a whole body scan by translating the patient through the PET camera. By projection the transverse section images a whole body overview can be made. An example is shown in Fig. 1 where in an oncological patient the glucose consumption is shown. A normal, high consumption in the brain and the heart (right image), a large tumor on the left image and two smaller on the right image are seen by their abnormal high glucose metabolism.

A PET center is the combined relevant knowledge of chemistry, medicine, pharmacy and physics and a PET center is staffed by all these disciplines in a good coopering team.

2. Possibilities of PET in research and patient care

The clinical applications of PET are in the fields of cardiology, neurology and oncology. In the cardiology the measurement of the myocardial blood under rest and stress conditions with ^{13}N-ammonia and the energy consumption with ^{18}FDG (^{18}F-fluorodeoxyglucose) is a standard examination in order to discriminate between isochemic and infarcted tissue. In the neurology the cerebral blood flow and/or the energy consumption of the brain is the standard examination. In the oncology PET is used for the detection of tumors and to measure the effect of therapy on the tumor metabolism.

In Table I different radiopharmaceuticals for cardiac studies are summarized. ^{13}N-ammonia is used for the measurement of the myocardial blood

TABLE I

Measurements and radiopharmaceuticals of importance for cardiology

Measurement	Radiopharmaceutical
Blood flow	$^{13}NH_3$, $H_2{}^{15}O$, ^{82}Rb
Metabolism	^{18}FDG, ^{11}C-fatty acids, ^{11}C-acetate
Receptor density	^{11}C-CGP
Hypoxia	^{18}F-fluoromisonidazol

flow. To study the viability of the heart it is used in combination with ^{18}FDG. The combination of ammonia rest, ammonia stress and metabolism study deliver a much too large number of images to evaluate individually. For this reason software to re-orient the images perpendicular to the long axis of the heart followed by a translation of the data into quantitative parameters of blood flow and glucose consumption per heart region has been developed. Blood flow and metabolism are than visualized per examination in a so called polar map. It also possible to use the electro-cardiac signals to make a gated cardiac study. From this data it is possible to generate images of the beating heart and if from these images the wall of the left ventricle can be detected, the wall motion can be quantified.

In Table II different radiopharmaceuticals for neuroscience studies are summarized. The clinical and research programs in Groningen are directed to glucose metabolism (^{18}FDG), protein synthesis rate (PSR) with ^{11}C-tyrosine [4] and blood flow with $H_2{}^{15}O$ [5]. The improvement in resolution can be seen in Fig. 2 where the glucose metabolism of the brain is shown for the different generations of PET scanners. For oncological studies both

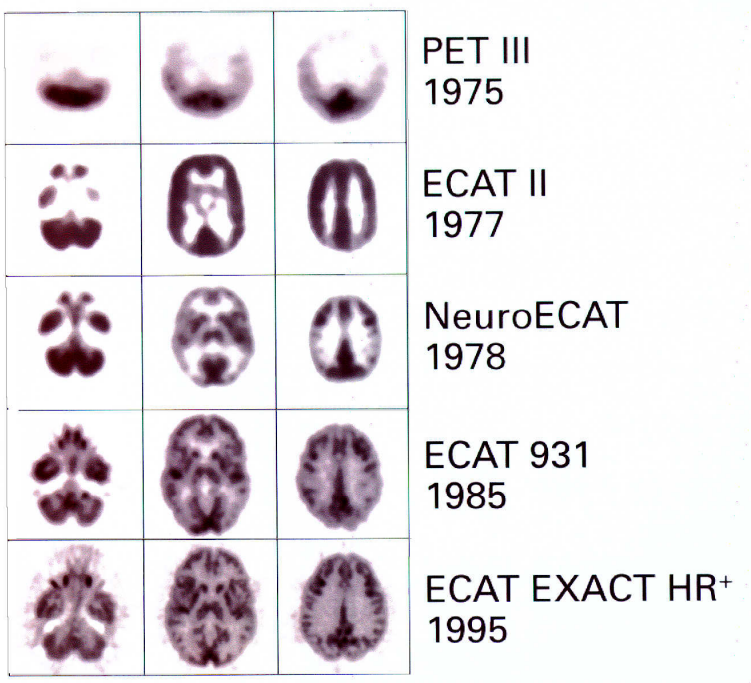

Fig. 2. The glucose consumption in the human brain as measured with FDG on the different generations of PET ring systems (Courtesy of CTI PET Systems, Inc.).

^{18}FDG as well as L-[1–^{11}C]tyrosine are available. Software for the translation of measured radioactivity into glucose-consumption (^{18}FDG) and protein synthesis rate of ^{11}C-tyrosine have been developed. The D_2 receptor in the human brain can be studied with ^{18}F-DOPA or ^{11}C-raclopride and is of importance in the case of Parkinson's disease. Measurement of the regional cerebral blood flow (rCBF) with $H_2{}^{15}O$ is of great importance to discover the functional anatomy in fields like cognitive neuroscience, linguistics, selective attention and to measure the effect of drugs on the rCBF in different categories of patients.

TABLE II

Measurements and radiopharmaceuticals of importance for neuroscience

Measurements	Radiopharmaceutical
Blood flow (rCBF)	$H_2{}^{15}O$, $C^{15}O_2$
Bloodvolume	^{11}CO, $C^{15}O$
Oxygen extraction	Combination of both above
Glucose metabolism	^{18}FDG
Tumor metabolism	^{11}C-amino acids, ^{18}FDG
Receptor measurements	^{11}C-methylspiperon, ^{18}FESP ^{18}F-DOPA, ^{11}C-raclopride
Stimulus research	^{18}FDG, $H_2{}^{15}O$

In Table III different radiopharmaceuticals for oncological studies are summarized. For the study of tumor metabolism ^{18}FDG is often used but other possibilities in the form of amino acids do exist. Also the effect of therapy on the tumor metabolism can be quantified by measuring before and after therapy. By performing the second study already during the therapy also a prognostic statement can be made. For oncological brain studies the use of an amino acid can be favourable due to the better signal to noise ratio which can be obtained with respect to the glucose metabolism study. It is also possible to generate "whole–body" images by projecting a number of consecutive transverse images into a planar image.

TABLE III

Measurements and radiopharmaceuticals of importance for oncology

Measurements	Radiopharmaceutical
Tumorperfusion	$^{13}NH_3$, $H_2{}^{15}O$
Tumormetabolism	^{18}FDG, ^{11}C-tyrosine, ^{11}C-methionine ^{11}C-thymidine
Cytostatica kinetics	^{11}C-cytostatica

3. New developments

The cyclotron as available now for PET centers is different from the older machines used in the field of nuclear physics not only because of the limited number of particles and fixed energy but also because of the incorporation of the targetry for the most important radionuclides. Automation and computer control is integrated into the design. Not only the beam quality but also the beam current is a major parameter because the current determines the production capacity. Beam quality is not that crucial for radionuclide production and in fact the beam power density (W/cm^2) should not be too high. For the day–to–day operation no separate operating team is required, the cyclotron can be operated by the technical chemical staff. The present developments tend into a few directions, but reduction in costs by *e.g.* a reduction in maximum beam energy is a general goal for the marketing of cyclotrons for clinical PET-centers. Reduction in maximum energy results in a smaller machine and consequently a reduction in costs is possible. Lower energy leads also to less penetrating particles and consequently to thinner targets with a lower yield. Consequently the target technology becomes more difficult and more critical by this reduction in beam energy because the beam current has to be increased to keep up in production capacity. The change to a superconducting magnet decreases the weight with a large factor. Since the production capacity should stay the same the thickness of the shielding is also the same but the overall size off the vault, and so the costs, can be decreased again. Some cyclotron manufacturers also provide local movable shielding of concrete and lead, fitting tightly around the accelerator, resulting in lower total mass of the shielding. Also developments in linear accelerators (linacs) and in Radio Frequency Quadrupole accelerators

(RFQ's) for the production especially of the four PET radionuclides, are taking place. However, it still has to be shown that this, may be cost effective solution, is a competitor in radionuclide yields with the now operating 17 MeV proton cyclotrons.

The radiation detectors used in positron cameras at the moment are made of BGO in most cases but also NaI and BaF_2 has been used or still is in use. Although BGO and BaF_2 have a high stopping power for 511 keV and a number of other favourable properties, the light yield of NaI is also favourable. The ideal detector for a positron camera should have a time resolution of approximately 10 ps and this combined with other properties like high stopping power, high Z, non hygroscopic *etc.* This extreme fast timing would allow for the measurement of the place of annihilation within a few millimetres by means of the time of flight (TOF) measurement. With the present detectors only the line on which the annihilation took place is being determined. The filtered back projection reconstruction technique in combination with block structure of the detectors makes a spatial resolution of 4–5 mm FWHM standard. Recently LSO (lutetium-orthosilicate) has been discovered as a scintillator [6]. LSO combines the good properties of BGO with high light yield (75% of the yield of NaI) and is also rather fast (40 ns). A disadvantage is the presence of natural radioactive isotope of lutetium but, since a coincidence technique is employed, this will not influence the image formation. The higher light yield will improve the energy resolution and by this decrease the scatter fraction. At the moment small LSO PET-scanners are being built for small animals (rats and mice) and a spatial resolution of 2 mm FWHM has been achieved in these systems. In the (near) future whole-body systems with this spatial resolution will become available.

The fundamental limit in the spatial resolution is of course the range of the positron itself. At the mean positron energy, 40 % of the maximum energy, the range of the positron varies from 1.1 mm for ^{11}C via 2.5 mm for ^{15}O to 5.9 mm for ^{82}Rb. At the moment interplane septa are used to limit the opening angle of each individual plane. This reduction of opening angle is necessary to keep the amount of scattered 511 keV γ-quanta within reasonable bounds. By removing these septa the efficiency of the whole system increases with a large factor but the fraction of scattered radiation will also increase. This is due to the rather bad energy resolution, 25% at 511 keV, of the BGO block detectors used. Nevertheless a lot of efforts has been invested in the development of systems without septa and in the development of correction algorithms for scatter, yielding a three dimensional imaging system [7].

The fact that the annihilation of positron and electron does not take place at zero momentum is proven by the fact that there is a finite angular width

of 0.5° FWHM in the angular distribution about the mean angle of 180°. With a detector ring diameter of roughly 80 cm and an improving spatial resolution this parameter is becoming more important as a limitation in the spatial resolution.

4. PET and other imaging modalities

The most common imaging technique in medicine uses X-rays. In its most simple form a density projection is generated by holding the subject of interest between the X-ray tube and a photographic plate. The advanced form can be found in a CT-scanner in which a rotating X-ray source and detectors make a transverse section image. Again sort of a density map is generated although extraction of the exact density will not be possible, and is also not necessary for diagnostic use, due to the broad energy spectrum of the generated X-rays. Due to the large difference in density between bones and tissue the bones can be visualized perfectly while small differences in tissue density will be more difficult to visualize. The use of contrast agents, like fluids with high densities and high Z-components, can change the difference in density and by this the interpretation of the images dramatically.

The Nuclear Magnetic Resonance (NMR) technique is in use to visualize the protons (bound to water) in the human body. Homogeneous magnetic fields up to 2 T are in use in medical NMR scanners, nowadays abbreviated to MRI (Magnetic Resonance Imaging). In order to have a short imaging time, gradient fields with frequency decoding are used. The strength of the NMR signal is proportional to the difference in population of the spin–up and spin–down state. Under normal conditions at room temperature the ratio between spin–up and spin–down is rather close to unity. The NMR technique is a rather insensitive technique [8] for this reason but which is successful because of the high water concentration in the human body. Also paramagnetic contrast agents like Gd-DTPA are used to increase the contrast. Both, the X-ray and the MRI technique, supply anatomical information.

With NMR also information on the structure of molecules can be obtained, as is done in the chemistry. This is also possible in the human body but limited to the brain and to molecular structures which have a concentration of 0.1 mM or more as a rule of the thumb. The limitation to brain tissue is because the signals from water and fatty tissues have to be suppressed and these concentrations are rather low in the brain in contrast to *e.g.* the thorax.

By using radionuclides bound to different molecular structures functional emission imaging became available in the 1950's. It is functional imaging because the chemical structure and the human metabolism determine the fate of the molecule in vivo. PET is the ultimate form of nuclear medicine.

Because the nuclear reactions for the production of positron emitting radionuclides are of the type (p, n) or (p, a) in most cases, the element produced is different from the target element. By this type of reactions the amount produced in weight is extremely low (1 Ci of ^{11}C has a weight of 1.2 ng) while the amount of radioactivity is considerable (1 Ci of ^{11}C can routinely be made and a patient dose is 10 mCi). This so called specific activity (MBq/mg) is of importance *e.g.* for receptor research and makes it possible to call it "tracer" experiments.

Since the PET method supplies functional information the combination with X-ray and NMR techniques, CT and MRI, would yield an identification of the functional anatomy. In order to make this combination the images of the different disciplines should be available in a transparent way and image resize and re orientation techniques should be available to match the images from the different modalities. At the moment there are no general applicable routines available to perform this kind of matching operations. In a number of PET centers the combination of PET , CT and NMR images is subject of interest. In some institutions also the comparison and transformation of PET images to a stereotactic brain atlas have been performed [5]. The head and brain are the first structure/organ of choice to evaluate the "multimodality" matching for obvious reasons.

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