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# Positron emission tomography (PET) in ischemic heart disease

**Karl Heinz Bohuslavizki, Winfried Brenner, Malte Clausen, Eberhard Henze**

*Clinic of Nuclear Medicine, Christian-Albrechts-University, Kiel, Germany*

*The key substrates of any biochemical pathway may be labelled by positron emitting nuclides, without interfering with their biological behaviour. These nuclides desintegrate with two gamma rays in opposite directions. Different kinds of PET cameras, their advantages and disadvantages are discussed in terms of geometric resolution, nuclides useable, costs, and logistic problems. Latest camera technology deals with SPECT camera capable of coincidence detection, thus allowing to perform PET images without large expenses for dedicated PET systems. This could turn FDG imaging towards just another simple nuclear medicine procedure. The main clinical benefit of this method lies in the proof of tissue viability in akinetic, hybernating myocardium prior to therapeutic interventions. Thus, for patient management PET will help to select the appropriate therapeutical procedure and thereby will increase the benefit-risk ratio for the patients.*

*Key words:* myocardial ischemia; tomography, emission-computed, positron emission tomography, PET; myocardial metabolism

## Introduction

Imaging procedures in nuclear medicine tend to be non-invasive, simple to perform once the equipment is available, and they produce a macroscopic display of the organ under investigation with a somewhat limited geometric resolution. The key message of nuclear medicine is visualizing both (patho-) physiology and metabolism.

In order to image pathophysiology and to charactarize the tissue under investigation small amounts of radioactive substances are incorporated into the patients and their distribution in the body is detected and analyzed over time. Single-photon emitters like technetium-99m, thallium-201, iodine-131, iodine-123, and indium-111 are the most often used radionuclides for labelling procedures. Once these nuclides are bound to a carrier the physicochemical properties of these carriers are altered, and therefore their metabolism is somewhat unphysiological. Thus, the challenge for the radiochemist with single-photon emitting nuclides is to produce radiopharmaceuticals, which despite of their unphysiological nature will detect clinically useful signals. This is the main limiting factor in the development of new tracers for conventional gamma camera techniques in nuclear medicine.

In contrast, with positron emitting nuclides completely physiological tracers may be developped, as shown in this paper.

Correspondence to: Dr. Karl H. Bohuslavizki, Clinic of Nuclear Medicine, Christian-Albrechts-University of Kiel, Arnold-Heller-Str. 9, D-24105 Kiel, Germany, Tel.: +49 431 597-3061, Fax.: +49 431 597-3150.

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## Positron emitters

The main advantage of these positrons radiated from the nucleus is their fate in tissue. Within a very short distance of about 1 mm the positrons collide with an electron and both corpuscles annihilate, vanishing completely. Their energy is transformed to electromagnetic radiation in a characteristic pattern. Two photons of exactly 511 keV each radiate from the site of collision in almost opposite directions. (To be more precise, the angle between the two photons is about 179 degrees. This fact together with the average length of radiation of the positrons

define the lowest possible limit of geometric resolution for physical reasons to about 2 mm). This allows for comparatively high resolution metabolic imaging with positron emission tomography (PET). Full width at half maximum is 5 mm for PET studies. In comparison, realistic data on full width at half maximum in SPECT studies is some 15 mm.

The most widely used positron emitting nuclides in PET-centers are given in Table 1. Obviously, positron emitting nuclides from nitrogen, oxygen and carbon are ideally suited for the design of radiopharmaceuticals with completely physiological behaviour ("make as small a change in the molecule to be traced as possible"). This opens tremendous possibilities for non-invasive, in-vivo autoradiographic analysis. In a specialized radiochemical laboratory any organic substrate of interest might be labelled, e.g. metabolites including analog substances, receptor ligands and drugs will react chemically and biologically in exactly the same way as their non-radioactive counterparts, due to their identical physico-chemical properties.

**Table 1.** Half-life of positron emitting nuclides commonly used.

| Nuclide | half-life [min] |
|---|---|
| Rb-82 | 1.26 min |
| O-15 | 2.07 min |
| N-13 | 9.96 min |
| C-11 | 20.40 min |
| F-18 | 109.70 min |
| Rb-81 | 274.80 min |

A characteristic feature of positron emitting nuclides is their short half-life in the range of minutes as depicted in Table 1. Therefore, for full utilisation of the PET technology an onsite cyclotron for the generation of short-lived nuclides and a radiochemical laboratory are required. The radiochemistry needed may be characterized by extremely fast synthesis and labelling techniques, essential for these (ultra-) short-lived tracers. Because of these expensive installations, costs have been reduced tentatively by supplying several tomographs by one cyclotron only. However, the main benefit of this shipment of short-lived nuclides might be for the inital phase of a newly installed PET-center.

On the other hand, the short half-life of these positron emitters puts a very small radiation burden on the patient, and investigations may be repeated in a short time before and following medication or therapeutic interventions. This fact is of special interest in diagnostic and therapeutic procedures in cardiology. By applying different tracers myocardial perfusion and blood pool, fatty acid metabolism, glucose utilisation (a marker of ischemia plus myocardial vitality) and the receptor status may be visualized successfully as shown in Table 2. An ideal tracer should clear fast from the background, should have a high myocardial uptake of sufficient duration for imaging, and shoult not influence metabolic pathways.

## Competing PET technologies

The common axis of the two photons of 511 keV may be seen by scintillation detector blocks with electronics, which is able to detect the corresponding pair of counts by their coincidence. These emitted projection data is then backprojected in a similar way as is done in X-ray computed tomography. Moreover, both machines look quite similar.

In modern PET systems a series of detector rings acquire three-dimensional data with high sensitivity, i.e. within a given angle any part of any ring may interact with any other part of any other ring for the coincident detection of the paired gamma rays. This technique will acquire simultaneously all data to cover an organ like the heart. Transmission

**Table 2.** Positron emitting nuclides in cardiology.

| | | |
|---|---|---|
| Circulation | N-13 $NH_3$ (ammonia) | blood flow |
| | Rb-82 | blood flow |
| | O-15 $H_2O$ | blood flow |
| | O-15 and C-11 CO | blood pool |
| Metabolism | C-11 palmitate | lipid acid metabolism |
| | F-18 deoxyglucose | glucose uptake |
| | C-11 acetate | Kreb's cycle / oxygen consumption |
| | C-11 amino acids | protein synthesis |
| | N-13 amino acids | protein synthesis |
| Neuronal receptors | C-11 quinucyclidine | ß-receptor ligand |
| | F-18 metaraminol | adrenergic innervation |
| | C-11 hydroxyephedrine | adrenergic innervation |
| Varia | F-18 misonidazol | detection of hypoxia |
| | Rb-81 | potassium pool |

**Table 3.** Comparison of tomographic systems in nuclear cardiology.

| | PET | SPECT + coincidence | SPECT |
|---|---|---|---|
| Tracer | physiological | physiological | non-physiological |
| Nuclides | short-lived | short-lived | long-lived |
| Nuclide distribution | restricted | restricted | widespread |
| Repeated studies | within hours | within hours | next day |
| Acquisition time (heart) | 10 min | 40 min | 20 min |
| Whole body capability | yes | no | limited |
| Resolution (FWHM) | 5 mm | 5 mm | 15 mm |
| Quantitation | precise | poor | poor |
| Availability | restricted | potentially widespread | widespread |
| Installation | 10 Mill US$ | 1 Mill US$ | 1 Mill US$ |
| Costs per investigation | 1200 US$ | 600 US$ | 300 US$ |

data are acquired for physically exact absorption correction. This allows to display the tracer distribution in Becquerel per volume and, therefore, serves as a basis for the calculation of quantitative physiological parameters.

In contrast, this is quite different in SPECT measurements. With single photons the count distribution correlates poorly with the activity distribution, and proves by experience only to be clinically useful as given in Table 3. However, the latest generation of multi-headed SPECT systems makes it possible to acquire transmission data as well. This SPECT transmission system allows for sufficient absorption correction while scatter remains a major problem. Superb images have been shown, but the clinical value of absorption correction in SPECT still remains to be evaluated.

Positron emission tomography is now around for about 15 years. However, the limited number of PET centers currently installed will not allow routine patient management on a broad basis. The high costs of the systems are due to rather sophisticated hardware required, especially when combining an on-site cyclotron and a radiochemistry with the PET scanner. The initial investment of a complete PET center will require 6–8 Mill US$ and the reimbursement for one investigation will approximate 1200 US$. These financial considerations will limit the technology to clearly defined clinical problems and especially to cardiological and brain research. To overcome these limitations, a new generation of low cost PET scanners are introduced by industry, e.g. ART-PET, which may change the benefit-cost ratio towards PET in the near future.

The latest camera technology came up with a machine in a somewhat intermediate position between PET and SPECT.[1] A double head gamma camera designed for excellent SPECT studies was equipped with high countrate capability and coincidence detection. Thus, PET and SPECT are achievable in a single gamma camera. After a potentially widespread installation this may allow tomographic examinations with physiological PET-tracers, i.e. fluordeoxyglucose (FDG), with the intrinsic good geometric resolution but without huge expenses necessary for dedicated PET centers. Since neither transmission measurements and consecutive quantification nor whole body imaging are feasable so far this system may become a worthwhile alternative in imaging of small organs as the heart and the brain.

In these organs, SPECT cameras equipped with high energy 511 keV collimators have been used. However, these images lack quality due to the rather limited geometric resolution of this system, with a possible role in cardiac studies only.

## Ischemic heart disease

Up to now only in a few PET centers worldwide basic research on myocardial ischemia in animal models has been performed. Subsequent clinical work has concentrated on myocardial ischemia and cardiomyopathies.[2, 3] Conclusive results using PET in ischemic heart disease are available only for the last two years with about 20–30 original papers based on studies with less than 200–300 patients in total, mostly performed in the US.

Normal myocardium utilizes fatty acids for its energy requirements during rest. At stress lactate acid from the skeletal muscle is taken additionally. During fasting state there is definitely no uptake of glucose in the myocardium. In contrast, the postprandial endogenous insulin load will result in glucose uptake of the myocardium as well. This pattern changes quite dramatically during ischemia. Even in the fasting state myocardial cells will switch towards anerobic energy production using glucose. This glucose uptake signals ischemic, but still viable myocardium. On the other hand, in scar tissue

there is very little uptake of any tracer because of its bradythophic metabolism.

In patients with ischemic heart disease PET may image non-invasively blood flow and metabolic parameters.[4] During hypoxia fatty acid metabolism is stopped and subsequently switched over to aerobic and anaerobic glycolysis, as desribed above. Using F-18 labelled FDG, increased glucose utilization may be detected in regional myocardial ischemia. This metabolic imaging may be combined with blood flow studies. Rb-82[5] and N-13-ammonia are commonly used blood flow tracers. With a double tracer technique of FDG and N-13-ammonia it seems possible to differentiate normal, scarred, and ischemic myocardium. In the latter there is decreased uptake of blood flow tracer while glucose utilization is enhanced, thus a "mismatch" between the two tracer patterns occurs. Infarcted myocardium may be identified by FDG (and C-11-palmitate) as a region of abolished metabolism.

## Myocardial vitality

Unexpected and partially spectacular results concerning demonstration of remaining vitality in akinetic myocardial regions, where no Tl-201 uptake could be shown in SPECT studies, have been reported. In one study, up to 58 % of persisting Tl-201 stress and rest perfusion defects interpreted as scar tissue showed metabolic residual activity with FDG in PET studies.[6] According to these results PET seems to allow prognostic statements concerning the prediction of contraction function of akinetic but still vital myocardial tissue after revascularization. This prediction was true in one study for 85 % of the patiens, whereas regions identified as scar tissue by N-13-ammonia and FDG-PET showed functional improvement in 8 percent only.[7] Therefore, the specificity for scar detection is high for PET, quite in contrast to SPECT studies performed with Tl-201.

However, two principal drawbacks underlying FDG-PET should be mentioned. There is no way to differentiate aerobic from anaerobic glycolysis, i.e. postprandially even normal myocardium shows FDG uptake. This has led to a variety of different acquisition protocols with no commonly accepted procedure so far. Furthermore, following myocardial infarction a solid block of scar tissue may be missing. Histologically, a mixture of scar fibres and still viable myocardial cells is demonstrated in these patients. Although these cells will show an increased FDG uptake, they remain immobilized by surrounding scar tissue. Therefore, following revascularization cardiac contraction will not be enhanced. Beside this clearly defined value for patients with ischemic heart disease in cardiological diagnostics, PET has a unique importance for clinical research due to the nearly unlimited possibilities of non-invasive in vivo investigations.[8]

## Ventricular tachycardia following myocardial infarction

One example will be given for current PET research in patients with ischemic heart disease. Following myocardial infarction some patients develop high risk ventricular tachycardias. The site of the arrhythmogenic substrate may be delineated by PET in two different ways. First, at the border of a myocardial scar ischemic myocardium is sometimes found. These areas are characterized by a perfusion – metabolism mismatch, i.e. reduced perfusion and enhanced glucose uptake. In exactly these areas, localized by PET, the electric focus during episodes of venticular tachycardia could be confirmed by elektrophysiologic studies.[9] Second, in a more specific approach the reuptake of adrenergic substances in nerve fibres of the myocardium may be documentated by PET.[10] Disturbances of this reuptake of adrenergic substances may signal membrane instabilities and, thus, a tendency towards arhythmia. In carefully controlled clinical studies it may be possible to link these findings of scintigraphically proven cardiac neuropathy with ventricular tachycardias and with the problem of sudden cardiac death.

## Conclusions

The main clinical benefit of PET in cardiology is to facilitate the prognosis of the success of any revascularization. By using a glucose derivate the viability of hybernating myocardium and thereby the curability may be proven. Otherwise, the impact of PET technology is concentrated mainly on basic research.

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