A NEW PET DIAGNOSTIC INDICATOR BASED ON THE RATIO OF $3\gamma/2\gamma$ POSITRON ANNIHILATION*

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The idea of applying the ratio of 3γ and 2γ positron annihilation rate as a diagnostic indicator in the PET imaging is proposed. It is based on the fact that the 3γ annihilation is related to the decay rate of triplet state of positronium atoms produced inside the human body during the PET imaging, and it reflects the size and the concentration of free volumes present in the investigated tissues. The tissues deformation related to the cancerous changes are expected to influence the local value of the 3γ fraction.

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1. Introduction

Physical phenomenon of positron annihilation is a base of a few experimental techniques used in various branches of science and life. For example, Positron Annihilation Lifetime Spectroscopy (PALS) is applied in materials science to investigate defects in metals, free volumes in polymers or pores in porous materials. One can follow such processes like face transition, hardiness, mechanical modification in presence of additives, pores fulfilling and many others [1, 2] using positron and positronium lifetime values. The other one, positron emission tomography (PET) is a well-recognized diagnostic method enabling imaging of the metabolism of chosen substances in

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living organisms [3, 4]. One of its many important applications is patient imaging aiming at the determination of the tumour location and size in the search for the possible metastases. The latter can be detected using PET even at the stages not detectable by other methods sensitive to anatomical or morphological changes. In order to perform PET imaging, a patient is administered a radiopharmaceutical containing radioactive atoms *e.g.* ^{18}F or ^{11}C, which emit a positron during a beta-plus decay. The current PET imaging is based on an annihilation of a positron (emitted by a radiopharmaceutical) with an electron (from the body of the patient) into two gamma quanta with the energy of 511 keV each.

Currently, PET technique is being developed in order to improve its time-resolution and compatibility with Magnetic Resonance Imaging [5–8] as well as to enable a simultaneous whole-body imaging [9, 10]. Such a development is carried out *e.g.* by the EXPLORER [9] or J-PET [10] collaborations. J-PET has developed a transportable and modular PET system that can be used also for multi-photon imaging [11]. This technique can be applied to improve the spatial resolution when using information from the prompt gamma emitted by the daughter nucleus produced in the decay of some beta-plus isotopes, for example, scandium-^{44}Sc: $^{44}\mathrm{Sc} \rightarrow^{44} \mathrm{Ca}^{*} e^{+} \nu_e \rightarrow^{44} \mathrm{Ca}\, \gamma e^{+} \nu_e$. In the radiopharmaceutical containing such isotope [12], a single decay undergoes with emission of three or four photons: two or three annihilation photons from the $e^{+}e^{-}$ annihilation and one prompt gamma from the deexcitation of the daughter nucleus. In order to take advantage of the prompt gamma, it was proposed to use a combination of the PET scanner and the Compton camera [13]. Another solution is possible with the J-PET scanner allowing for the registration of annihilation photons and prompt gamma with the strips of plastic scintillators arranged axially. In reference [14], a method which uses a prompt photon for the determination of the time of a positronium formation inside a human body and annihilation photons to determine the moment of its disintegration, was described. For each recorded event, a prompt deexcitation gamma is registered in order to determine a time of creation of the positronium atom and, in addition, two or three annihilation photons are measured to determine the time of the decay of this atom. The combined information from prompt and annihilation photons enables us to reconstruct the image of positronium lifetime $\tau_{\mathrm{o-Ps}}(x, y, z)$ and the image of its production probability $P_{\mathrm{poz}}(x, y, z)$ [14]. These properties of positronium and their combination may serve as a diagnostic indicator in addition to the Standardized Uptake Value (SUV) presently available in PET. Interestingly, as shown in [14] in the case of $\tau_{\mathrm{o-Ps}}$ and P_{poz} images, it is not needed to perform attenuation corrections that are necessary for reconstruction of metabolic image and SUV index.

However, a solution of morphometric imaging described in Ref. [14] is restricted to radiopharmaceuticals with isotopes emitting prompt gamma and excludes usage of the most popular PET isotopes as *e.g.* ^{18}F or ^{11}C which changes upon the positron emission into ground state of their daughter nuclei and do not emit a prompt gamma quantum. In this article, we described a new method which shall allow to determine diagnostic indicators based on the properties of positronium independently whether the radiopharmaceutical is labelled with isotope which emits prompt gamma or not [15].

2. Processes of positron annihilation

The positron produced during β^+ decay of radioactive nuclei inside the matter can generally annihilate with emission of $n\gamma$ quanta. Free positron annihilation occurs predominantly into two gamma quanta, and only about $1/372$ of direct positron annihilations results in the emission of three gamma quanta. However, thermalized positron can also create a positronium (Ps) with an electron from the body. Ps can exist in two spin states: para-positronium (p-Ps) and ortho-positronium (o-Ps) with a spin equal to 0 and 1, respectively. Both states are unstable and decay in vacuum with the mean lifetime values of 125 ps (p-Ps) and 142 ns (o-Ps) [16, 17]. In the dense matter, such atoms can be produced and trapped in the free volumes between molecules. In vacuum, the ortho-positronium atom decays predominantly into three gamma quanta, however, inside the diagnosed patient it may also disintegrate via emission of two gamma quanta *e.g.* due to the pick-off process [18]. In effect, o-Ps in the examined object decays in two ways: some fraction by intrinsic decay into 3γ and another one into 2γ via pick-off process. Fractional rate of these competing processes depends on the void size, the larger is the void volume, the higher is the lifetime value and the higher is the 3γ fraction $f_{\mathrm{o-Ps-3}\gamma}$. According to the model presented by Tao [19] and Eldrup *et al.* [20], one can correlate the o-Ps lifetime value obtained from PAL spectra with the size of free space. If the size of the voids is of the order of an angstrom, then $\tau_{\mathrm{o-Ps}}$ is very sensitive to small fractional changes in their size or shape [21, 22]. Thus, the probability of creation and lifetime of ortho-positronium should be related to the morphology of the cells and may be used as an indicator of the stage of a development of morphologic disorders. Such correlations have been recently reported in a few papers [23, 24].

3. Proposal of the new diagnostic indicator

The fraction $f_{\mathrm{o-Ps-3}\gamma}$ of o-Ps atoms annihilating with the emission of 3γ quanta in the body can be described by a following equation:

$$f_{\mathrm{o-Ps-3}\gamma} = \tau_{\mathrm{o-Ps}}/\tau_{\mathrm{o-Ps-vacuum}}\,, \tag{1}$$

where, $\tau_{\mathrm{o-Ps-vacuum}}$ denotes the o-Ps lifetime value in the vacuum, equal to 142 ns. In the case when only one kind of free volumes/pores exists in the material, the 3γ fraction in the whole spectrum can be effectively described by the equation:

$$f_{3\gamma} = \frac{\left(1 - \frac{4}{3}P_{\mathrm{o-Ps}}\right)}{372} + \frac{\tau_{\mathrm{o-Ps}}}{\tau_{\mathrm{o-Ps-vacuum}}} P_{\mathrm{o-Ps}}\,, \tag{2}$$

where $P_{\mathrm{o-Ps}}$ (equal to 4/3 of o-Ps component intensity determined from the lifetime spectrum) denotes the ortho-positronium formation probability, which also depends on the molecular structure of the investigated object.

The relationship presented above was successfully applied to investigate high-porosity materials, prepared to use in some experiments for material targets [25–30]. We propose to apply determination of 3γ fraction for investigation of biological media/human body tissues containing small free volumes (Jasińska *et al.* [31]).

As it was described above, the 3γ fraction also reflects the size and the concentration of the free volume. Then we propose here to use the variation of the fraction $f_{\mathrm{o-Ps-3\gamma}}$ as a new diagnostic indicator. The variation of the fraction $f_{\mathrm{o-Ps-3\gamma}}$ manifests itself in the variation of the ratio $f_{3\gamma 2\gamma} = N_{3\gamma}/N_{2\gamma}$ of positron–electron annihilation rates into 3γ and 2γ quanta. The $f_{3\gamma 2\gamma}$ fraction can be determined experimentally as a ratio of the number of 3γ and 2γ events emitted from the investigated object during imaging using, in general, all kind of PET scanners equipped in 3γ coincidence system. This can be done *e.g.* by means of the J-PET scanner [10, 11]. The $f_{3\gamma 2\gamma}$ ratio can be correlated with $f_{3\gamma}$ expressed in Eq. (2) by the following formula:

$$f_{3\gamma 2\gamma} = \frac{f_{3\gamma}}{1 - f_{3\gamma}}\,. \tag{3}$$

The possibility of a simple recalculation of the results obtained using PALS in terms of the above introduced indicator allows to perform monitoring of experiments of various kind of tissues.

4. Conclusions

The proposed new diagnostic indicator based on $3\gamma/2\gamma$ positron annihilation ratio is a measure of the degree of the tissue porosity in the investigated organism and can serve for the description of the advancement of the cell abnormalities. The proposed indicator in the form of 3γ and 2γ ratio is a parameter independent on the time of patient investigation and local radiopharmaceutical concentration. It is also independent on the 2γ imaging and may deliver an additional information to the standard PET indicators

from the data received simultaneously during a single PET investigation. It is important to notice that the $3\gamma/2\gamma$ indicator may be determined for all PET radioisotopes including the most popular ^{18}F and ^{11}C.

The proposed method should give valuable results for whole body PET scanners as they have much higher spatial acceptance resulting in much higher efficiency for the detection of 3γ in comparison to the current PET scanners.

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