Biological washout effect in in-beam PET: animal studies

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Abstract. Positron emission tomography (PET) is a practical tool for range verification of hadron therapy. As well, the quantitative washout of the positron emitters has a potential usefulness as a diagnostic index, but the modelling for this has not been established. In this study, we measured washout rates of rabbit brain and performed kinetic analysis to explore the washout mechanism. Six rabbit brains were irradiated by \textsuperscript{11}C and \textsuperscript{15}O ion beams, and dynamic PET scan was performed using our original depth of interest (DOI)-PET prototype. The washout rate was obtained based on the two-compartment model, where efflux from tissue to blood (k\textsubscript{2}), influx (k\textsubscript{3}) and efflux (k\textsubscript{4}) from the first to second compartments in tissue were evaluated. The observed k\textsubscript{2}, k\textsubscript{3} and k\textsubscript{4} of \textsuperscript{11}C were 0.086, 0.137 and 0.007 min\textsuperscript{-1}, and those of \textsuperscript{15}O were 0.502, 0.360 and 0.007 min\textsuperscript{-1}, respectively. It was suggested permeability of a molecule containing \textsuperscript{11}C atoms might be regulated by a transporter. The k\textsubscript{2} of \textsuperscript{15}O was comparable with \textsuperscript{15}O-water. This study provides basic data for modelling of the washout effect.

1. Introduction
The advantage of charged particle therapy is that the charged particles deposit the highest dose near the end of the beam path, at the Bragg peak. Because of the sharp dose gradients near the Bragg peak, beam range uncertainty is of concern. A positron emission tomography (PET) method has been applied as an \textit{in-vivo} range verification. The main contributors for \textit{in-vivo} PET range verification for particle therapy are \textsuperscript{11}C (T\textsubscript{1/2}=20.39 min) and \textsuperscript{15}O (T\textsubscript{1/2}=122.2 s). The positron emitters induced by treatment beam irradiation, however, are not static but are diffused or perfused in living tissue due to biological processes during irradiation and PET imaging, which degrades the correlation between activity and delivered dose distribution. Correction for the biological washout effect is the major issue for clinical use of \textit{in-vivo} PET range verification. Also, despite the biological washout process being an unfavourable effect which causes uncertainty for dose verification, it could be exploited to provide insights into physiological changes during the course of treatment. The biological washout model should

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be established. In this study, we measured washout rates of rabbit brain and performed kinetic analysis on dynamic PET data to explore the biological-washout mechanism.

2. Material and Methods

2.1. Experimental setup
Radionuclide beams of $^{15}$O and $^{11}$C were irradiated on rabbit brains in the secondary beam lines of the Heavy Ion Medical Accelerator in Chiba (HIMAC). The biological washout rate for a total of 6 rabbits (3 for $^{11}$C beam irradiation and 3 for $^{15}$O beam irradiation) was measured by our original whole-body depth-of-interaction (DOI)-PET prototype [1] which allows detection of positron emitters with good statistics. Figure 1 shows the experimental setup and simplified drawing. The detector ring (660 mm in diameter) was positioned perpendicular to the beam direction to enable in-beam PET. A rabbit was fixed in an acrylic cylinder and connected to an anesthesia machine. PET scans were performed for 40 min for $^{11}$C beam irradiation and 20 min for $^{15}$O beam irradiation. The acquired data were divided into frames with 30 s duration. For each frame, the ordered subset expectation maximization method (OSEM) algorithm was applied. The reconstructed image was fused with the computed tomography (CT) image. The volumes of interest (VOIs) were selected based on the heart and lung region, and the time activity curves (TACs) were generated.

![Figure 1](image1.png)

**Figure 1.** The experimental setup with 4-layer DOI-PET prototype for rabbit brain irradiation: a photo (a) and a simplified drawing (b).

2.2. Analysis
The two-compartment model commonly used in nuclear medicine was employed to derive the biological washout rate [2,3]. The tissue is composed of 2 compartments and $k_2$ is efflux from the tissue to blood, $k_3$ and $k_4$ are influx and efflux from the first to the second compartments. $K_1$ represents the rate constant between arterial blood and tissue. However, because we assumed almost all implanted $^{15}$O and $^{11}$C ions were stopped in the tissue, we did not include $K_1$. Radioactive concentrations of the first ($C_{T1}$) and second ($C_{T2}$) compartments of tissue without $K_1$ are expressed as equations (1) to (3). Here, $I_1$ and $I_2$ are initial radioactivities of the respective compartment. So radioactivity concentration of the total tissue is expressed as equation (4). Because we assumed $I_2$ was negligible, it was not included to fit the experimental TAC. Consequently, the fitting process is described as equation (5) and (6). Then, comparative review of the derived parameters in this study with that of other PET pharmacokinetic studies was performed.

$$C_{T1} = I_1 [(k_2 - \alpha_1) \exp(-\alpha_1 t) - (k_4 - \alpha_2) \exp(-\alpha_2 t)]/(\alpha_2 - \alpha_1) \quad (1)$$
\[ C_{72} = I_1 k_4 \{ \exp(-\alpha_1 t) - \exp(-\alpha_2 t) \} + I_2 \exp(-k_4 t) / (\alpha_2 - \alpha_1) \quad (2) \]

\[ \alpha_{2,2} = \left( \frac{(k_2 + k_3 + k_4)}{\sqrt{(k_2 + k_3 + k_4)^2 - 2k_2k_4}} \right) / 2 \quad (3) \]

\[ C_7 = C_{71} + C_{72} = I_1 \left[ (k_3 + k_4 - \alpha_1) \exp(-\alpha_1 t) - ((k_3 + k_4 - \alpha_2) \exp(-\alpha_2 t) + I_2 \exp(-k_4 t) \right] / (\alpha_2 - \alpha_1) \quad (4) \]

\[ N[p \cdot \exp\left\{ -(\lambda_{phys,cont} + \alpha_1) \cdot t \right\} + (1 - p) \cdot \exp\left\{ -(\lambda_{phys} + \alpha_1) \cdot t \right\} + R[p \cdot \exp\left\{ -(\lambda_{phys,cont} + \alpha_2) \cdot t \right\} + (1 - p) \exp\left\{ -(\lambda_{phys} + \alpha_2) \cdot t \right\} \quad (5) \]

\[ R = (k_2 + k_4 - \alpha_2) / (k_2 + k_4 - \alpha_1) \quad (6) \]

3. Results

Figures 2 (a)-(d) show 2-dimensional spatial distributions in two rabbits measured by our whole-body DOI-PET prototype (10 min PET images). The arrows in the figures show the beam direction. Implanted radioactive ion beams into the brain were diffused to the whole body due to the biological washout effect in the living condition (Figure 2 (a) and (c)).

TACs for VOI of $^{15}$O and $^{11}$C beam irradiation with fitting results using the 2-compartment model are shown in Figure 3. As the result of comparative review of the delivered parameters with other PET pharmacokinetic studies, $k_2$ obtained from $^{15}$O beam irradiation was close to that of $^{15}$O-water in cerebral blood flow. And $k_2$ obtained from $^{11}$C beam irradiation model suggested permeability of the generated molecule with $^{11}$C regulated by a transporter, because efflux from the tissue was relatively low compared with simple diffusion tracers. The $k_3$ values of $^{11}$C and $^{15}$O were much higher than $k_4$ values, thus part of the $^{11}$C and $^{15}$O ions were fixed in the tissue.

![Figure 2](image-url)

**Figure 2.** Coronal slices acquired by the whole-body DOI-PET prototype (summed 0-10 min after irradiation) fused with CT images. PET images of $^{15}$O beam irradiation under the live condition (a) and the dead condition (b), and $^{11}$C beam irradiation under the live condition (c) and the dead condition (d). For comparison of appearance of signal diffusion by the biological washout effect, the colour scale of each PET image was normalized according to the half-life of $^{11}$C and $^{15}$O.
4. Conclusion

We measured the biological washout rate of implanted $^{15}$O and $^{11}$C ion beams in rabbit brain. Using our whole-body DOI PET prototype, we demonstrated dynamic analysis. The 2-compartment model fitted the experimental TAC well. A careful determination of chemical forms containing the $^{15}$O and $^{11}$C atoms is essential to investigate the biological washout mechanism and to use the biological washout rate as a clinical diagnostic index. This study provided useful data for modelling the biological washout effect.

5. References

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