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Metabolic Studies of ^{11}C in Rabbit Thigh Muscle Implanted by Secondary Beam of HIMAC

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INTRODUCTION

The accuracy of dose distribution in heavy ion therapy is dependent on the range estimation of projectile ions in the target medium. Heavy ion range is estimated from the measured CT number by looking up a measured conversion table. Since CT number is related to X-ray absorption coefficient that consists of photoelectric effect, coherent scattering and incoherent scattering, it is a complicated function of electron density and atomic number. The range of heavy ion is a function of the electron density of the medium. This leaves some ambiguities in this conversion and some sorts of experimental checking means are needed. With β^+ emitting ion beam, we can measure their end points by measuring annihilation pair γ rays with a positron emission tomography (PET) or a positron camera. End point distribution of positron emitting beam provides us such a checking means. In our institute, ^{12}C beam produced by HIMAC has been in use for heavy ion therapy. The secondary beam generator/separator was built last year and phantom experiments had been performed at the end of last year. ^{11}C beam was selected, since its LET is the same as that of ^{12}C and its half life is 20.39 minutes and is appropriate for the measurement. One ambiguity of the use of positron emitting radioactive beam to this end is the metabolism of implanted ^{11}C inside the living objects. We already measured the metabolism of ^{11}C activity generated through autoactivation of ^{12}C beam. In the latter case, activity level is quite low, since ^{11}C is the product of fragmentation reaction of ^{12}C beam, while the dose is limited by ^{12}C beam theraphy. With the same dose, ^{11}C beam allows us about 50 times higher activity and thus the accuracy of ^{11}C metabolism is higher. We performed metabolic rate measurement of ^{11}C inside the thigh muscle of rabbits focusing our attention to the existence of faster component in clearance.

METHOD

Secondary beam generation and separation

An apparatus to produce radioactive isotope beam is illustrated in Fig. 1. ^{12}C primary beam is bombarded on a thick Be target, in which secondary particles of variety of nuclides are generated through fragmentation reaction. The energy of fragments at the target exit depends on the point of reaction, since energy loss through the rest of the target depends on the interaction point. The first bending magnet and slit pair analyzes them according to A/Z. The energy degrader placed behind the first slit along with the second bending magnet achieves achromatic focusing at the exit. The second slit further analyzes nuclides according to Z. Two pairs of bending magnet and slit achieves good elemental separation, $A/\Delta A$. The spatial spread of the secondary beam at the focus point is about 1 cm in FWHM. The purity of the secondary beam depends on the width of the slit and the slit adversely limits the

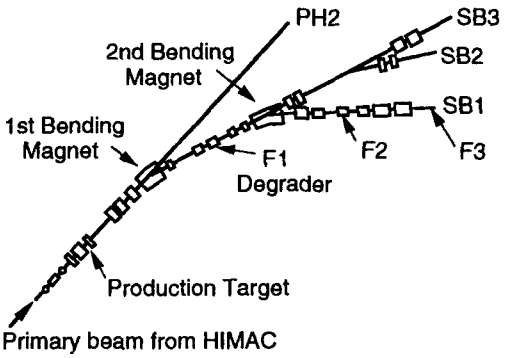

Fig. 1. Illustration of secondary beam generator/ separator.

yield. Typical yield of ^{11}C out of ^{12}C is 0.5% with 98 % purity. ^{12}C primary beam energy was selected to 290 MeV/u and a Be target of 51 mm thick is in use. An Al energy degrader of 3.5 mm average thick were used resulting ^{11}C energy of 184 MeV/u.

Irradiation Setup of ^{11}C beam

Experimental setup is shown in Fig. 2. The primary beam intensity was monitored by an in-beam SEC (secondary emission counter) monitor and the secondary beam intensity was monitored by a thin plastic scintillator (Bicron BC400, 5 mm thick). Events were recorded by a preset counter that controls beam ON and OFF. Counting technique is not accurate even at low beam intensity due to the beam spill structure of synchrotron. One beam spill consists of many micro beam pulses of short duration, which implies that pulse pile-up is higher than usual counting of radiation from radioisotopes. Beam intensity must be high enough to shorten the irradiation time, since implanted ^{11}C decays during irradiation. The beam intensity was about $1x10^5$ particles per sec. Correction of pulse pile-up from statistical consideration is inaccurate because beam intensity fluctuates. Therefore, monitoring of beam intensity with a plastic scintillation counter was calibrated with a SEC prior to the irradiation. SEC linearity has proven from 10^5 to 10^9 pulses/ sec. ^{11}C beam was first collimated by an Al block of 5 cm thick with a 6 cm square hole that shields extra area of the plastic scintillator and further collimated by a brass block of 6 cm thick with a 2 cm square hole. A small laser pointer was aligned to the beam axis by a transit scope and then a cross-hair cursor printed on an OHP sheet was aligned to the laser beam. In the case of irradiation, the rabbit was adjusted so that the mark on the rabbit skin was aligned to the laser pointer and then the laser pointer was displaced lower so as not to intervene the beam. The laser pointer can be repositioned by shifting it up to the position at which the laser pointer hits the cross-hair cursor.

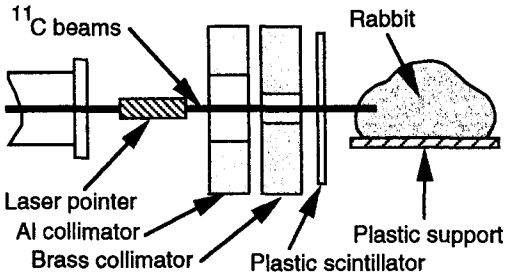

Fig. 2. Experimental setup of ^{11}C irradiation to rabbits.

Irradiation of ^{11}C and PET measurements

The rabbit was anesthetized by an intramuscular injection of a mixture of Ketamine (anesthesia, 37.5 mg/kg) and Xylazine (muscle relaxant, 5 mg/kg), then hairs at the irradiation spot were removed and the rabbit was fixed on a PMMA board. Occasionally, additional anesthetics were given to maintain anesthesia. The rabbit was irradiated with quasi-monochromatic ($\Delta p/p \approx 1\%$) beam of ^{11}C. Total number of particles was $1.75x10^7/cm^2$, which corresponds to physical dose at maximum of 9.3 Gy. The rabbit was transported to PET (model HR+, Siemens) and emission scan was measured in dynamic study mode at 2 minutes' interval for 60 minutes. Then it was sacrificed by an injection of KCl and transmission scan was done for 30 minutes. Three point sources of ^{18}F were attached to the surface of the rabbit and the emission scan was done for 10 minutes. The rabbit was transported to X-CT and was scanned to image anatomical structure. These point sources can be imaged with X-CT to correct for scaling factor and rotation of the two kinds of images. The experimental plan on rabbits was undergone the inspection of the committee on ethics of animal experiments set in our institute and was approved. The same rabbit in dead condition was irradiated with ^{11}C beam of $1.75x10^7/cm^2$ particles with the same irradiation setup to see the distribution without metabolism. This measurement allows us to ascertain the relative activity level without critical calibration of PET sensitivity. Since transportation of the rabbit and its setting to PET took us about 10 minutes, the initial decay of the live rabbit could not be measured. The irradiation dose was higher than the value in real situation but kept low to prevent acute radia-

tion hazard that may disturb normal metabolism. Dynamic measurement allows us to adjust the statistics by selection of number of slices and time duration after irradiation.

To see the time-activity curve just after the irradiation, other experiments were performed using a positron camera that can be set in the beam line. The camera consists of two Anger cameras of thick crystals. This camera is longitudinal tomography and the information along the camera axis is lacking in contrast to PET, so that quantification capability is not enough, but sufficient to measure the time-activity curves.

RESULTS

In the PET measurement, emission data were corrected for random coincidence and scattered rays. The emission images of ^{11}C in a rabbit in live (left) and dead (right) conditions are shown in Fig. 3, in which they are superimposed on the transmission images of the same slices to show the body boundary. The activity outside the target region is so low that body boundary can hardly be seen in the emission image. This is probably because target region is much small compared to total body, so that the activity recirculated to the slice is quite low. The emission images of the live

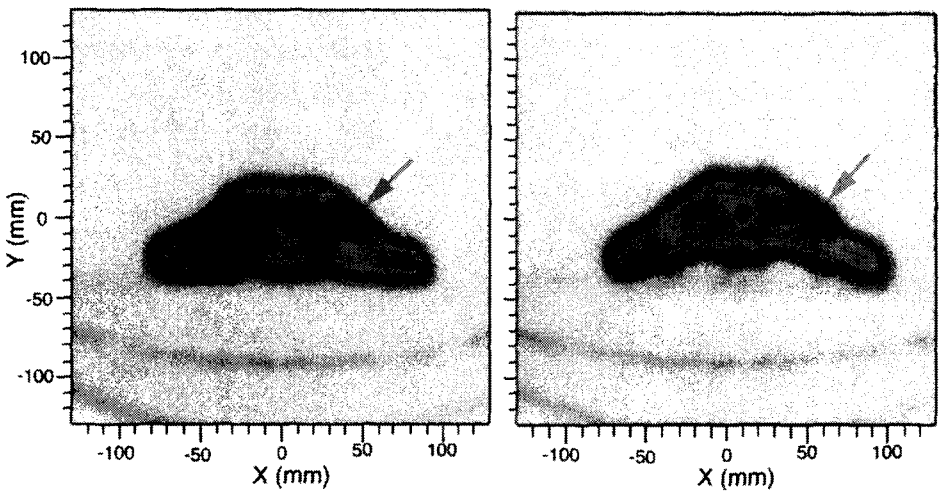

Fig. 3. Emission images of ^{11}C superimposed on transmission images for live (left) and dead (right) conditions. Red arrows indicate accumuration of ^{11}C activity.

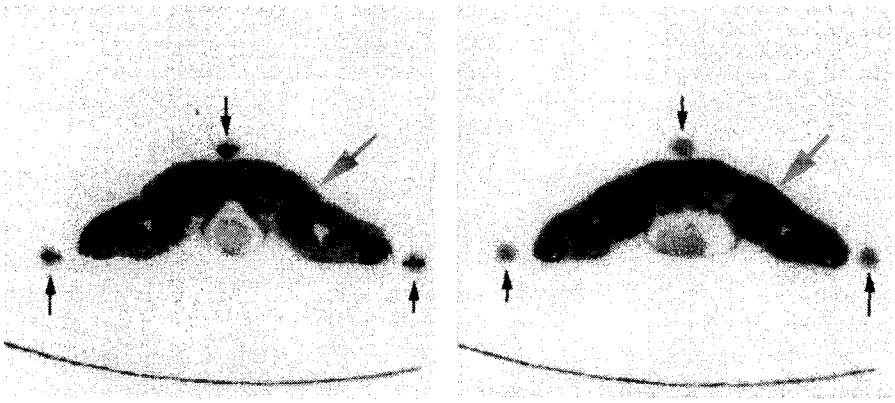

Fig. 4. Emission images of ^{11}C superimposed on marker images and X-CT images for live (left) and dead (right) condition. Red arrows indicate accumulation of ^{11}C activity, while blue arrows indicate locations of reference sounces.

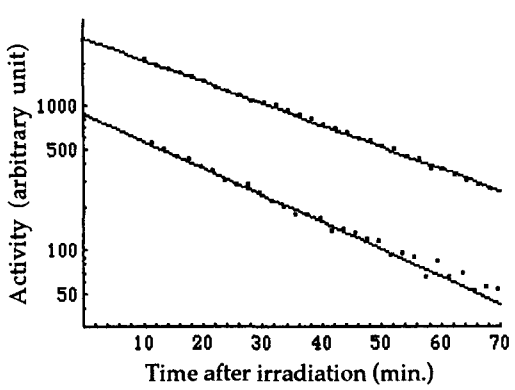

Fig. 5. Time-activity curves inside the ROI in live (lower) and dead (upper) conditions measured with an off-site PET.

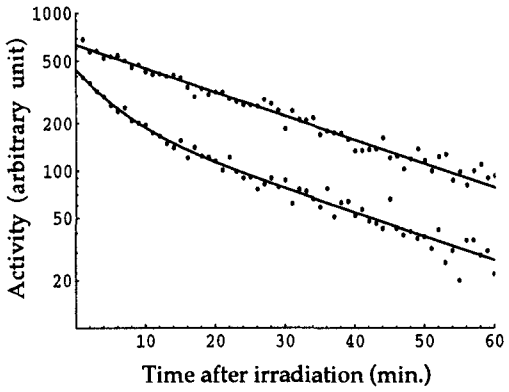

Fig. 6. Time-activity curves in live (lower) and dead (upper) measured with a positron camera insitu.

rabbit superimposed on X-CT images are shown in Fig. 4. The active marker images are also shown for reference. The results of time-activity analyses are shown in Fig. 5. Measured half-life of the dead rabbit was 20.3 minutes (cf. physical half-life of ^{11}C is 20.39 minutes), while that of the live rabbit was 16.0 min. from which biological half-life is 74 minutes and is about 4 times longer than physical half-life. Another finding is that the estimated initial activity of the live one is about 1/3 of the dead one, which suggests the existence of faster component. Due to the time for transportation of the rabbit from irradiation site to PET site, earlier transition cannot be measured with an off-site PET.

Earlier clearance could be observed with a positron camera set in beam line. Counts in region-of-interest (ROI) versus time are shown in Fig. 6. It revealed the existence of the fast component. Biological half-life of the slow component is 89 min. and the ratio of initial activity in dead condition to that in live condition was 2.9. Biological half-life of the earlier phase was 15.2 min.

DISCUSSION

Even with the insitu measurement, the initial activity of the live rabbit is 2/3 of that in the dead rabbit. This indicates the existence of even faster third component that could not be measured due to the finite irradiation time, since the faster component may be washed out during irradiation time of ~ 1 minutes. The third component may be attributed to blood flow whose half-life is supposed to be about seconds in the case of rabbits.

In the past, we studied autoactivation and measured the biological half-lives of ^{11}C in the thigh muscle of rabbits, in which ^{12}C beam was irradiated and ^{11}C activitiy was generated through projectile fragmentation and target fragmentation of ^{12}C inside the target. Biological half-lives of two such experiments were 75 and 95 minutes. The present results roughly agree with those of autoactivation studies, because physiologic behavior must be the same in both cases in spite of the difference in the ^{11}C implantation.

CONCLUSION

From the time-activity analysis of ^{11}C beam irradiation, the measured biological half-lives turned out 74 and 89 minutes for two cases and are about 4 times longer than the physical half-life of ^{11}C, which ensures us the imaging of implanted ^{11}C distribution. Biological half-life may vary among organs, since constituent and metabolism may vary. Existence of fast clearance component was observed. About 1/3 of activity can be imaged about 10 minutes after the irradiation with an off-line PET. From the insitu positron camera measurements, existence of faster component was suggested. The component may be attributed to blood flow, however its origin could not be ascertained at present.