# Dosimetry for 6-[18F]Fluoro-L-DOPA in humans based on *in vivo* microPET scans and *ex vivo* tissue distribution in mice

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## Introduction

Radiation dosimetry of new radiopharmaceuticals generally starts with studies in small animals such as mice and rats. The traditional technique has long been *ex vivo* measurement of the biodistribution over time using harvested organs at different times post administration of the radiopharmaceutical. Since this approach requires a significant amount of animals, dynamic microPET studies, where the complete biodistribution of the tracer over time can be determined *in vivo* in a single scan, are an invaluable alternative. Due to known imaging artifacts and limitations, such as partial volume effect, a hybrid technique combining harvesting organs (post-scan) and dynamic imaging was introduced to achieve a cross-calibration to account for these limitations.

## Materials & Methods

The tissue distribution over time of 6-[18F]Fluoro-L-DOPA was determined by:

1) Radioassay of harvested organs in isoflurane-anaesthetized mice:

- Brain, heart, kidneys, liver, lung, spleen and testes
- At 2, 5, 10, 30, 60, 120 minutes post injection, n=4 at each time point
- Average bodyweight 23.5 ± 1.75 g; Average injected activity 8.47 ± 1.45 MBq

2) Dynamic PET imaging acquired using a FOCUS 120 microPET over 120 minutes after injection of 6-[18F]Fluoro-L-DOPA followed by radioassay of harvested organs in isoflourane-anesthetized mice (n=4). CT images were obtained using a GE eXplore 120 micro-CT prior to dynamic PET imaging:

- Time frames: 6x5s, 6x10s, 3x20s, 5x30s, 5x60s, 8x150s, 6x300s, 6x600s.
- Average bodyweight 22.1 ± 1.21 g; Average injected activity 7.66 ± 1.62 MBq

Clearly identifiable organs were manually segmented in the reconstructed co-registered PET/CT images and organ time-activity-curves (TACs) were obtained. TACs from PET were multiplied with the cross-calibration factor between PET activity and Gamma counter activity levels.

TACs from both methods were extrapolated from a simulated 35 g standard mouse to a 70 kg standard male human using a technique based on organ to bodyweight ratios [Kirschner et al., 1975]:

$$\left[\left(\frac{\%}{g_{organ}}\right)_{animal} x(kg_{TB\ weight})_{animal}\right] x \left(\frac{g_{organ}}{kg_{TB\ weight}}\right)_{human} = \left(\frac{\%}{organ}\right)_{human}$$

A bladder voiding scenario was used to simulate excretion every 2 h. The absorbed doses in major human organs were calculated using the extrapolated TACs with the commercially available human dosimetry software OLINDA/EXM (Version 1.1).

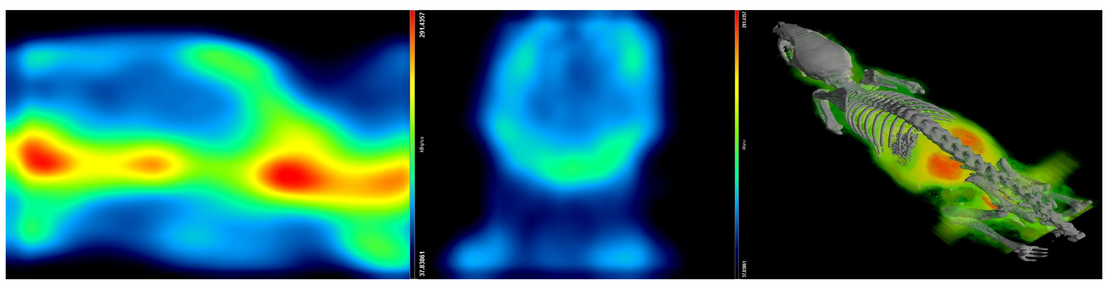

**Figure 1 – Brain uptake and 3D representation of co-registered micro PET/CT image (left: sagittal plane through brain and skull, middle: coronal plane through brain and skull, right: 3D segmentation)**

## Results

- TACs were derived using the tissue distribution and the hybrid technique, average correlation coefficient between TACs r = 0.94 ± 0.05, p < 0.001

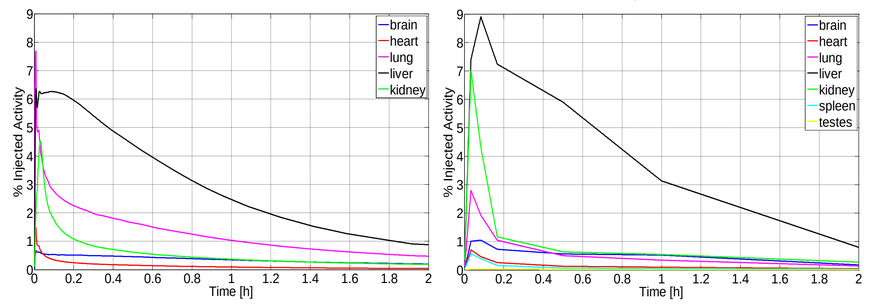


**Figure 2 – Human average TACs derived with hybrid technique (left) and derived from tissue distribution (right)**

- Differences at high activity levels were revealed in Bland-Altman plots for TACs with a correlation below r = 0.94 (lung 0.91 and heart 0.85)

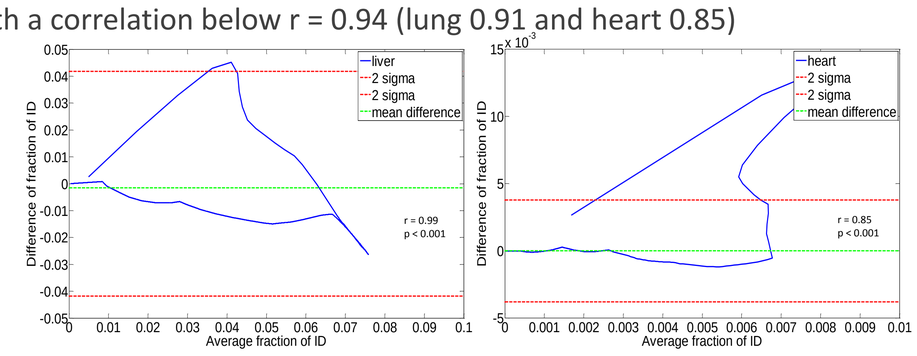


**Figure 3 – Bland-Altman plots of Liver TACs (left, highest correlation) and Lung TACs (right, lowest correlation)**

- Residence times and doses were calculated for a standard 70kg male human using both methods

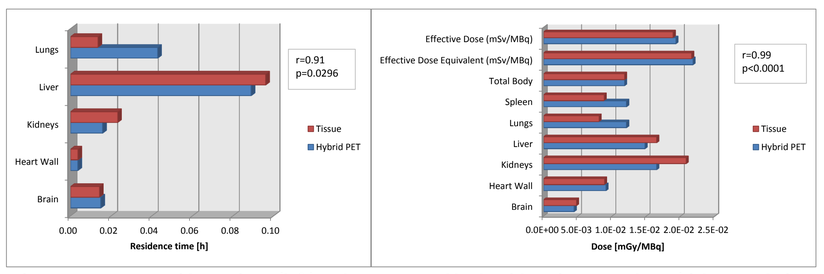


**Figure 4 – Average residence times (left) and average total body with major organ doses (right, correlation calculated for all dose values, not just major organs)**

- The highest doses were received by organs in excretion pathways comprising bladder (0.142 mGy/MBq both methods), kidneys and liver (see Figure 4)
- The effective total body dose was 0.0193 mSv/MBq for hybrid and 0.0189 mSv/MBq for pure harvesting based method

## Conclusions

Scaling errors in the PET TACs are likely caused by quantification errors such as partial volume effects and image artifacts, which caused an underestimation in activities measured by microPET imaging only in brain, heart and lung (mean: 30%, 10% and 28%, respectively) and an overestimation in kidney and liver (mean: 21% and 30%). The use of the hybrid imaging technique to cross-calibrate the TACs improved the accuracy of the imaging-based dosimetry estimates. Therefore the hybrid technique combining dynamic imaging and harvesting organs (post-scan) is a suitable alternative to the gold standard *ex vivo* radioassay method using harvested organs at different time points. It yields comparable results yet reduces significantly the amount of animals needed in the study and can accelerate data acquisition.

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