Comparison of first pass bolus AIFs extracted from sequential ^{18}F-FDG PET and DSC-MRI of mice

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Abstract

Accurate kinetic modelling of in vivo physiological function using positron emission tomography (PET) requires determination of the tracer time-activity curve in plasma, known as the arterial input function (AIF). The AIF is usually determined by invasive blood sampling methods, which are prohibitive in murine studies due to low total blood volumes. Extracting AIFs from PET images is also challenging due to large partial volume effects (PVE). We hypothesise that in combined PET with magnetic resonance imaging (PET/MR), a co-injected bolus of MR contrast agent and PET ligand can be tracked using fast MR acquisitions. This protocol would allow extraction of a MR AIF from MR contrast agent concentration-time curves, at higher spatial and temporal resolution than an image-derived PET AIF. A conversion factor could then be applied to the MR AIF for use in PET kinetic analysis. This work has compared AIFs obtained from sequential DSC-MRI and PET with separate injections of gadolinium contrast agent and ^{18}F-FDG respectively to ascertain the technique's validity. An automated voxel selection algorithm was employed to improve MR AIF reproducibility. We found that MR and PET AIFs displayed similar character in the first pass, confirmed by gamma variate fits ($p<0.02$). MR AIFs displayed reduced PVE compared to PET AIFs, indicating their potential use in PET/MR studies.

1. Introduction

Positron emission tomography (PET) is a quantitative imaging technique with very high sensitivity and specificity, making it ideally suited to functional investigations of tissue metabolism. Image quantitation can be performed using standard uptake values (SUVs) [1], but more accurate, relevant parameters can be obtained with compartmental modelling of tracer kinetics [2]. Although these models differ in complexity depending on the tracer used, all require knowledge of an arterial input function (AIF) to extract accurate rate constants linking the compartments. The AIF is defined as the tracer time activity-curve (TAC) in arterial plasma and is ideally measured from an artery feeding the ROI. This measurement can be performed clinically via invasive blood sampling (e.g. ~1-2ml samples throughout the scan) or non-invasively by extracted an activity time course from arterial voxels on dynamic PET images.

In preclinical imaging, however, the low total blood volume (e.g. ~2ml in mice [3]) requires specialist equipment [4-6] to extract blood samples safely and even then may disturb the system under measurement. Non-invasive methods are therefore preferred, although the small size of the mouse makes it difficult to place an ROI in the blood pool of the heart [4]. Furthermore, partial volume effects (PVE) contaminate the measurements, typically reducing the peak height and increasing the width of the AIF peak [7]. As yet, no consensus has been achieved in preclinical studies for the extraction of image-derived AIFs accurately and reliably.

Simultaneous PET/MR can be used to combine the comparatively high temporal and spatial resolution of dynamic MRI imaging to assist in non-invasive AIF extraction from dynamic PET. We hypothesise that a co-injected bolus of MR contrast agent and PET ligand can be tracked with fast MR acquisitions. This protocol would allow extraction of a MR AIF from MR contrast agent concentration-time curves which could then be converted to a PET AIF for use in kinetic analysis.

The concentration-time curve of a gadolinium-based MR contrast agent has previously been used to model PET tracer TACs in plasma [8]. The MR and PET AIFs analysed by Poulin et al. were found to adopt a similar shape in the first pass but diverge in the long decay phase. The conversion between MR and PET AIFs therefore had to be conducted via empirically-derived factors for the rodent cohort.

In the present study, we have focused on the first pass bolus of the tracer to ascertain how similar the contrast agent and tracer curves are between modalities in the initial injection phase. Echo planar imaging (EPI) sequences have been used in a dynamic susceptibility contrast (DSC)-MRI protocol [9] to detect the passage of contrast agent through murine arteries and veins via a change in the R2* relaxation parameter, which is proportional to the change in gadolinium-based contrast agent.

It is difficult, however, to reliably identify blood vessel voxels in DSC-MRI due to the low SNR of EPI acquisitions. Manually selecting voxels to extract an AIF is therefore vulnerable to human error and low reproducibility [10]. Automatic AIF determination algorithms have been developed to solve this problem [11-13] and an application of one such algorithm on the DSC-MRI data is presented here. This work hopes to give an indication of whether first pass MR data can be used to improve PET AIF determination and subsequently increase the accuracy of PET kinetic analysis.

2. Materials and Methods

Sequential PET and MRI Four mice were imaged sequentially using DSC-MRI on a 4.7T Bruker Biospin 47/40 scanner and dynamic PET on the Cambridge Split Magnet PET/MR scanner [14-15]. A bolus of 0.3mM/kg gadolinium contrast agent (Gd-BT-D03A) bolus was administered to each mouse via the cannulated tail vein 10s into a 100s single shot GE-EPI sequence (TR/TE 250/9ms, spatial resolution $110\times200\mu m^2$, 5 slices, thickness 1.5mm, 400 frames, 100s acq. time). The animal bed was then transferred to the Focus 120 PET camera housed in the PET/MR scanner and a 10 minute transmission scan performed with a ^{68}Ge source. A second injection of 30MBq ^{18}F-FDG was then injected through the same tail vein cannula. A 1 hour dynamic PET emission acquisition in listmode was reconstructed as dynamic data frames (3D FBP: 30x1s, 30x5s, 12x10s and 11x300s) with randoms, dead time, decay, detector efficiency, scatter and attenuation corrections applied. The scanner spatial resolution was 1.8mm isotropic (FWHM) at the centre of the FOV. The reconstructed image dimensions were 128×128×95, with an in plane resolution of 0.866mm and a slice thickness of 0.796mm. Figure 1 depicts the imaging protocol for each mouse.

INSERT FIGURE 1 (1.5 column width)

Automated MR arterial voxel selection A progressive voxel inclusion scheme [16-18] utilising prior knowledge of arterial positioning was applied to each mouse DSC dataset. A database of angiography scans was used to create a voxelwise probability map for murine blood vessels (256×256×128, isotropic resolution 250μm, thickness 0.2mm). The processing and transformation of the prior knowledge map into mouse native space is shown in Figure 2. This map was transformed to each subject using the SPMmouse toolbox [19].

INSERT FIGURE 2 (1 column width)

A rectangular ROI which encompassed the posterior cerebral artery (PCA) was selected as a starting point for an iterative voxel selection algorithm. AIF characteristics were ranked and starting threshold values determined empirically for each parameter. The algorithm applied the following steps to the MR contrast agent concentration-time curves:

Step 1) Select voxels in ROI with rise time <3s
Step 2) Peak height > 90^{th} percentile
Step 3) Area under the curve (AUC) >10^{th} percentile and first moment <50^{th} percentile
Step 4) FWHM < 50^{th} percentile

Prior knowledge from the vascular atlas was then applied, selecting voxels with a probability >0.2 of being a major blood vessel. The thresholding method was then re-applied, iteratively adjusting the threshold values (e.g. changing 90^{th} to 95^{th} percentile for peak height threshold) for each mouse until <10 voxels remained. The application of this algorithm is illustrated in Figure 3.

INSERT FIGURE 3 (2 column width) AND FIGURE 4 (1 column width)

AIF comparison MR AIFs were extracted as the mean signal from 5 voxels with the largest signal heights which survived all thresholds. For the PET data, a volume of interest (VOI) for the left ventricle was drawn on the final frame of each dataset using a manually seeded growth algorithm in the ASIPro software provided with the scanner (Siemens Medical Solutions, USA, Inc., Knoxville, TN, USA). These VOIs were projected onto all frames and PET AIFs were extracted as the mean signal from the VOI in each frame, as shown in Figure 4.

PET and MR AIFs were compared by aligning the flush peaks of the curves and normalizing the areas under curves (AUC) for the first 90s or setting the peak heights to 1. MR AIF data was also averaged into the PET temporal resolution and compared to the PET curves.

3. Results

Arterial voxel detection Automatic voxel selection method provided AIFs with more consistent peak heights and curve shapes, compared to manual selection. The MR AIF data was analysed to give estimates of relative CBF, CBV and MTT [9]. The distribution patterns of rCBF and rCBV agreed with literature, as well as the mean absolute MTT values (this study: 6.6 ± 3.1s, DSC-MRI cohort of additional 19 WT mice (data not shown): 5.9 ± 1.3s, literature: 6.3 ± 1.5s) [20-21]. This validated the MR image derived input functions as suitable AIF estimates.

Curve Comparisons Gamma variate fits were successfully performed on both MR and PET AIFs and are shown in Figure 4 for the AUC normalization. Goodness of fit was confirmed with p values <0.02 using the Chi-squared test. Increased agreement between the curves (see Figure 5) was seen as the peak height of the MR AIFs was reduced after averaging the MR AIF data into the PET temporal resolution. Figure 6 shows the MR (6(a)) and PET (6(b)) AIFs for all 4 mice, as well as the MR AIFs averaged into the PET temporal resolution (6(c)). A comparison of the population (mean) MR and PET AIFs in the PET temporal resolution is shown in Figure 6(d).

INSERT FIGURE 5 (1.5 column width) AND FIGURE 6 (1.5 column width)

4. Discussion

The MR AIFs show that preclinical AIFs are improved in a similar manner to clinical AIFs if voxel selection is automated [11-13]. The decreased variation in the MR AIFs after application of prior knowledge derived from angiography recommends the use of the algorithm in future studies.

Whilst similar shapes are confirmed in the first pass by fitting gamma variate functions, the peaks of the first pass were much taller and thinner from the MR AIFs when compared to the PET AIFs in the AUC normalization. This was confirmed by the peak height normalization, where the tails of the PET curves remained at a much higher level over the course of the scan. Both normalizations show similar arterial characters in the peak region but differences seen between the curves appear characteristic of PVE in the PET data. This difference was still observed if the MR data (0.25s resolution) were smoothed into the PET temporal resolution of 1s. The difference between the curves was attributed to contaminating the AIF with tissue TACs, resulting in the apparent lower peak height.

Whilst these results are encouraging, it must be noted that there was variability between the PET curves due to different volumes of tracer being injected and additional variability in both sets of curves due to manual administrations of the bolus injections. These obstacles could be avoided in future experiments with a syringe pump and a co-injection of tracer and contrast agent to ensure that the MR and PET protocols truly measure the same AIF. Ideally this should be conducted on a simultaneous PET/MR scanner.

5. Conclusions

Image derived first pass bolus AIFs derived from sequential PET/MR were found to be of similar character. The data suggest that MR AIFs are more precise due to reduced PVE. We are confident that

they can be used in simultaneous PET/MR once appropriate scaling factors have been derived via blood sampling.

6. Acknowledgments

This work was funded by an MRC studentship and travel to PSMR 2013 was funded by the EU COST action for PET/MR.

7. References

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Figure Captions

Figure 1: Sequential PET/MR protocol outline. Injections conducted from outside magnet bore via tail vein cannula. TRX = transmission scan, AC = attenuation correction

Figure 2: Probabilistic vascular atlas. (A) Sample mouse brain TOF angiography scan, which is co-registered to common space template in SPMmouse using T2w anatomical scans to compute transformation matrix. (B) Normalization in common space to create probabilistic map of vessel positions. (C) Inverse transformation of prior knowledge information into subject space.

Figure 3: Workflow of automated algorithm, incorporating iterative thresholding and prior knowledge to estimate the MR AIF.

Figure 4: Axial PET image of mouse heart (left), with blood pool VOI used for AIF extraction highlighted in yellow. A magnified (×10) image is shown on the right.

Figure 5: Individual mouse PET and MR image-derived AIF comparison. Gamma variate fits (left) to PET and MR curves (AUC normalization) indicate similar bolus shapes. Reducing the temporal resolution of the MR AIF to that of the PET AIF (right) by smoothing shows increased agreement between the curves.

Figure 6: AIFs for 4 mice using AUC normalization (a) MR, (b) MR smoothed into PET space and (c) PET. Population AIFs for (b) and (c) are compared in (d), error bars indicate one standard deviation.