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Image Derived Input Function for Cerebral PET Studies: Summary, discussion and future perspectives

Summary

This thesis describes the development and evaluation of a non-invasive method for obtaining the input function. Extraction of arterial input functions from dynamic brain scans may obviate the need for arterial sampling and would increase the clinical applicability of quantitative PET studies. Different strategies for extracting image derived input functions (IDIF) from dynamic PET images were evaluated. To correct for partial volume effects, a reconstruction based partial volume correction (PVC) method was implemented. Optimal settings for extracting the input function and for the reconstruction based partial volume correction were evaluated for a number of tracers with different kinetics. Methods were evaluated for both standard and high resolution scanners. For all tracers, image derived input functions were compared with measured arterial input functions. As IDIFs are sensitive to patient motion, effects of this motion, together with different motion correction methods, were evaluated.

In **chapter 2**, the evaluation of different methods for extracting image derived input functions from dynamic [^{11}C]flumazenil PET scans is described. Optimal settings were determined for a reconstruction based PVC method that was used for extracting the image derived input functions. Best results were obtained from reconstruction based PVC images, using 4 iterations, 16 subsets and a resolution kernel of 4.5 mm full width at half maximum (FWHM), which represents the point spread function of the scanner. It was demonstrated that a region of interest (ROI) consisting of the four hottest pixels per plane (over the carotid arteries) was the best method to extract IDIFs. Excellent peak area under the curve (AUC) ratios (0.99 ± 0.09) between IDIF and blood sampler input function (BSIF) were found. In addition, extracted IDIFs provided volume of distribution (V_T) and K_1 values that were very similar to those obtained using BSIF. The proposed method appeared to be suitable for analysing [^{11}C]flumazenil data without the need for on-line arterial sampling.

In **chapter 3**, an evaluation of the optimal image derived input function extraction method for [^{11}C]flumazenil PET brain studies obtained using the high resolution research tomography (HRRT) is provided. As these PET images have higher spatial resolution, optimal settings for extracting IDIFs and for the reconstruction based PVC were determined again. In addition, the impact of high resolution on accuracy of image derived input functions was assessed. Good peak AUC ratios (0.83 ± 0.21) between IDIF and BSIF were found for IDIFs that had been extracted from standard HRRT reconstructed images and that had been scaled (calibrated) to manual samples. In addition, good slope values (1.07 ± 0.11) were found. Improved resolution, as obtained with PVC reconstruction, changed AUC ratios between IDIFs and BSIFs to 1.14 ± 0.35 and, for tracer kinetic analysis, slopes changed to 0.95 ± 0.13. For all reconstructions, non-scaled IDIFs gave poorer results ($>61 \pm 34\%$ higher slopes) compared with calibrated IDIFs. The results of this study indicated that the use of IDIFs, extracted from OP-OSEM or PVC OP-OSEM images, is also fea-

sible for dynamic HRRT data, thereby obviating the need for on-line arterial sampling.

In **chapter 4**, the robustness of the image derived input function extraction method, developed in chapter 2, was assessed for three additional tracers ([^{11}C]PIB, *(R)*-[^{11}C]verapamil and *(R)*-[^{11}C]PK11195) with varying brain uptake. Again, IDIFs derived from PVC reconstructed images were compared with BSIFs using AUC ratios and outcome of tracer kinetic analyses. For *(R)*-[^{11}C]verapamil, accurate IDIFs were obtained (slope: 0.96 ± 0.17; R^2: 0.92 ± 0.07) without scaling to manual samples. However, scaling was necessary to make IDIFs comparable to BSIFs for both [^{11}C]PIB (slope: 1.04 ± 0.05; R^2: 1.00 ± 0.01) and *(R)*-[^{11}C]PK11195 (slope: 0.96 ± 0.05; R^2: 0.99 ± 0.01). The need for calibration may be due to stickiness of both tracers, in which case BSIFs may have been affected by sticking. Nevertheless, results of this study showed that the method to extract image derived input functions is also suitable for [^{11}C]PIB, *(R)*-[^{11}C]verapamil and *(R)*-[^{11}C]PK11195 studies, thereby obviating the need for on-line arterial sampling.

In **chapter 5**, the accuracy of reconstruction based PVC was validated using both phantom and clinical studies. The NEMA NU2 Image Quality phantom and five healthy volunteers (using [^{11}C]flumazenil) were scanned on both HR+ and HRRT scanners. HR+ data were reconstructed using normalization and attenuation weighted ordered subsets expectation maximization (NAW-OSEM) and a PVC algorithm (PVC-NAW-OSEM). HRRT data were reconstructed using 3D ordinary Poisson OSEM (OP-OSEM) and a PVC algorithm (PVC-OP-OSEM). For clinical studies, parametric volume of distribution (V_T) images were generated. For phantom data, good recovery was found for both OP-OSEM (0.84 to 0.97) and PVC-OP-OSEM (0.91 to 0.98) HRRT reconstructions. In addition, for the HR+, good recovery was found for PVC-NAW-OSEM (0.84 to 0.94), corresponding well with OP-OSEM. Finally, for clinical data, good correspondence was found between PVC-NAW-OSEM and OP-OSEM-derived V_T values (slope: 1.02 ± 0.08). This study showed that HR+ image resolution using PVC-NAW-OSEM was comparable to that of the HRRT scanner. As the HRRT has a higher intrinsic resolution, this agreement validates reconstruction-based PVC as a means of improving spatial resolution of HR+ scanner and therefore improving quantitative accuracy of PET.

In **chapter 6**, four different off-line frame-by-frame methods to correct for patient motion were evaluated. These methods differed in the way realignment parameters were derived. Two simulation studies were performed, based on [^{11}C]flumazenil and *(R)*-[^{11}C]PK11195 datasets, respectively. For both simulation studies, different types (rotational, translational) and degrees of motion were added. Simulated PET scans were corrected for motion using all correction methods. The optimal method derived from these simulation studies was used to evaluate two (one with and one without visible movement) clinical datasets of [^{11}C]flumazenil, *(R)*-[^{11}C]PK11195 and [^{11}C]PIB. For each dataset, V_T was derived using Logan analysis and values were compared before and after motion correction. For both [^{11}C]flumazenil and *(R)*-[^{11}C]PK11195 simulations, optimal results were obtained when realignment was based on non-attenuation

corrected images. For the clinical datasets motion disappeared visually after motion correction. Regional differences of up to 433% in V_T before and after motion correction were found for scans with visible movement. On the other hand, when no visual motion was present in the original dataset, overall differences in V_T before and after motion correction were $<1.5 \pm 1.3\%$. In conclusion, frame-by-frame motion correction using non-attenuation corrected images improved accuracy of tracer kinetic analyses compared to non-motion corrected data.

In **chapter 7** the effects of motion affected IDIFs on the outcome of tracer kinetic analyses were quantified. Two simulation studies, one based on high and the other on low cortical uptake, were performed. Different degrees of rotational and axial translational motion were added to the final frames of simulated dynamic PET scans. Extracted IDIFs from motion affected simulated scans were compared to original IDIFs and to outcome of tracer kinetic analysis (V_T). Differences in IDIF values of up to 239% were found for the last frames. Patient motion of more than 6° or 5 mm resulted in at least 10% higher or lower V_T values for the high cortical tracer. The degrees of motion studied are commonly observed in clinical studies and hamper the extraction of accurate IDIFs. Therefore, it is essential to ensure that patient motion is minimal and corrected for.

General discussion & future perspectives

Validation of image derived input functions

According to common practice, the (externally measured) arterial input function was used as gold standard for validating the accuracy of IDIFs. It can be questioned, however, whether this is a valid approach, i.e. whether an externally measured arterial input function can really serve as the gold standard. In routine practice, there are a number of problems with externally measured input functions. Firstly, the arterial input function is not measured at the location of interest, i.e. the brain, but at the radial artery. Therefore, the arterial should always be corrected for delay and dispersion. Secondly, problems with failed cannulations or clogged lines in ∼5% of the cases lead to study rejection. Finally, sticking of the tracer to the wall of the tube, as is possibly the case with [^{11}C]PIB, will result in overestimations of arterial concentrations. In theory, the IDIF approach does not suffer from these problems and potentially could provide a more accurate description of the true arterial input function, provided count statistics are not too low and appropriate corrections for partial volume and patient motion are in place. In general, it is difficult to validate any method for deriving IDIF as long as the 'gold standard' is not entirely reliable. At present, however, there is no other option than to use the externally measured arterial curve. It is therefore important to assess the accuracy of the arterial input function in advance. In addition, arterial input functions should always be corrected for the stickiness of the tracer.

A disadvantage of the method developed in this thesis is the fact that for some tracers manual arterial samples were still necessary for obtaining accurate results. In fact, manual arterial samples are needed for almost all tracers, as the whole blood curve derived from the images still needs to be corrected for plasma-to-whole blood ratios and labelled metabolites in order to obtain the true metabolite corrected plasma input function. Future work should focus on the use of venous instead of arterial samples. This would increase patient friendliness and thereby facilitate clinical use of quantitative PET studies. In addition, alternative methods for measuring metabolites, as mentioned in chapter 2, should be investigated.

Obtaining the image derived input function

The proposed method for obtaining the input function from dynamic PET images is simple and applicable to a large range of tracers. The studies described in this thesis, however, illustrate that for some tracers it is necessary to scale the IDIFs to manual blood samples, whilst for others this is not needed. Inaccurate scatter correction (HRRT) and stickiness of some tracers (e.g. [^{11}C]PIB) may be the reason for a varying correlation with arterial input functions. These problems may hamper the validation and the direct applicability of IDIFs to other tracers then the ones used in this thesis. It is therefore recommended to validate the use of IDIFs for other tracers. In addition, for clinical use, it is necessary to validate (per tracer) the robustness of the method on a larger dataset (n=20–30), preferable in a test-retest setting. Use of the proposed method for obtaining the input function from the images themselves is not restricted to brain studies alone. It will be of interest to assess the proposed method also for myocardial and oncological PET studies.

Reconstruction based partial volume correction

An important finding of this thesis is that, for standard clinical PET scanners, more accurate IDIFs may be obtained when images are reconstructed using a partial volume corrected reconstruction algorithm. Settings for the point spread function (PSF), used in the present reconstruction based partial volume correction, were optimized for the region of the internal carotid arteries, the area of interest for extracting IDIFs. However, these PSF settings cannot always be used for other (brain) regions, as the PSF of a PET scanner is not uniform throughout the field of view. The resolution is best in the centre of the field of view and deteriorates towards the edge. One solution would be to determine the PSF again for the area of interest and use that value in the reconstruction based partial volume correction method. A more advanced method would be to determine the PSF for the whole field of view and use this position dependent PSF during the reconstruction. This would make it possible to use the reconstruction based partial volume correction method for any region of interest without first having to determine the location of the area of interest. This

is not only important for defining IDIFs, but also for defining tissue data with higher resolution.

Motion correction

Patient motion is one of the main limiting factors in dynamic PET studies in general and for defining IDIFs in particular. The work in this thesis shows that patient motion may lead to large and significant errors of tracer kinetic analyses, primarily due to mispositioning of the IDIF ROI. Motion affected dynamic PET scans, however, may be corrected accurately using off-line frame-by-frame motion correction methods as described in chapter 6. The main limitation of off-line motion correction methods is that is not possible to correct for in-frame motion. This is especially important for frames towards the end of the scan, which typically last 5–10 min. For data obtained with older PET scanners, without the possibility of acquiring list-mode data, there is no other solution than to correct data frame-by-frame. For datasets that are scanned in list-mode, but without the use of an on-line optical tracking system, a more accurate correction for motion may be achieved by dividing large frames into several smaller frames; i.e. 5×2 min frames instead of 1×10 min frame. After motion correction, these short frames may be summed again to obtain sufficient statistics. In summary, the most accurate method to correct for patient motion is to use an on-line motion tracking system, as in-frame motion may be corrected for. However, when such an on-line motion tracking system is not available, the use of a frame-by-frame motion correction method provides major improvements in accuracy of pharmacokinetic analyses over non-motion-corrected data.

Apart from the limitation that it is not possible to correct for in-frame motion, the best motion correction method in this thesis is also based on some important assumptions. One of the main assumptions is that there is no mismatch between the transmission scan and the first couple of frames of the dynamic PET scan. However, if no motion is present between transmission and emission scans, the use of the optimal frame-by-frame motion correction method (chapter 6) resulted in more accurate results compared to non-motion-corrected data. As a mismatch between transmission and emission scan is not inconceivable, future work should focus on a frame-by-frame motion correction method that also corrects for a transmission-emission mismatch.

Conclusion

The use of motion corrected PET images together with reconstruction based partial volume correction enables the extraction of image derived input functions as an alternative for arterial sampling. This, in turn, will facilitate the use of quantitative PET studies in routine clinical practice.