Quantification of $^{18}$F-fluorocholine kinetics in patients with prostate cancer

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Word count: 4982

Short running foot line: Quantification of $^{18}$F-fluorocholine
ABSTRACT

Choline kinase is upregulated in prostate cancer (PCa), resulting in increased $^{18}$F-fluoromethylcholine uptake. This study utilizes pharmacokinetic modeling to validate the use of simplified methods for quantification of $^{18}$F-fluoromethylcholine uptake in a routine clinical setting. **Methods:** 40min dynamic PET/CT scans were acquired after injection of 204±9MBq $^{18}$F-fluoromethylcholine, from eight patients with histologically proven metastasized PCa. Plasma input functions were derived using continuous arterial blood sampling (BSIF) and image-derived (IDIF). Manual arterial blood samples were used for calibration and correction for plasma-to-blood ratio and metabolites. Time activity curves (TAC) were derived from volumes of interest (VOI) in all visually detectable lymph node metastases (LNM). $^{18}$F-fluoromethylcholine kinetics were studied by non-linear regression fitting of several single- and two-tissue plasma input models to the TAC. Model selection was based on Akaike’s information criterion (AIC) and measures of robustness. In addition, the performance of several simplified methods, such as standardized uptake value (SUV) was assessed. **Results:** Best fits were obtained using an irreversible compartment model with blood volume parameter. Parent fractions were 0.12±0.4 after 20min, necessitating individual metabolite corrections. Correspondence between venous and arterial parent fractions was low as determined by the intraclass correlation coefficient (ICC=0.61). Results for IDIF derived from VOI in blood pool structures distant from tissues of high $^{18}$F-fluoromethylcholine uptake, yielded good correlation to those for BSIF ($R^2=0.83$). SUV showed poor correlation to parameters derived from full quantitative kinetic analysis ($R^2<0.34$). In contrast, lesion activity concentration normalized to the integral of the blood activity concentration over time (SUV$_{AUC}$) showed good correlation ($R^2=0.92$ for metabolite corrected plasma and $R^2=0.65$ for whole-blood activity concentrations). **Conclusion:** SUV cannot be used to quantify $^{18}$F-fluoromethylcholine uptake. A clinical compromise could be SUV$_{AUC}$ derived from two consecutive static PET scans, one centered on a large blood pool structure during 0-30min p.i. to
obtain the blood activity concentrations, the other a whole body scan at 30min p.i. to obtain LNM activity concentrations.

**Keywords:** positron emission tomography (PET), prostate cancer, choline, tracer kinetic modeling, standardized uptake value (SUV)
INTRODUCTION

Prostate cancer (PCa) is one of the most commonly diagnosed neoplasms in men worldwide and incidence is increasing (1). Accurate diagnostic procedures are essential, as therapeutic options vary greatly with extent of the disease (1,2). Conventional imaging techniques, including transrectal ultrasound, computed tomography (CT) and magnetic resonance imaging, are used routinely in PCa, but their diagnostic accuracy is suboptimal (3).

Positron emission tomography (PET) provides a very sensitive and accurate non-invasive method to study metabolic activity of tumor tissue in vivo. The most commonly used oncological PET tracer, fluorodeoxyglucose (18F-FDG), shows limited sensitivity for the detection of androgen dependent PCa (4). In contrast, encouraging results have been published using both 11C and 18F labeled choline derivatives as PET tracers for PCa (5-9).

The amino acid choline is an important precursor for the biosynthesis of phosphatidylcholine, a key component of the cell membrane phospholipids. Following transport into the cell, choline is phosphorylated by choline kinase to phosphocholine and trapped within the cell (10). Most types of cancer, including PCa, are characterized by increased choline transport and over-expression of choline kinase, in response to enhanced demand of phosphatidylcholine in highly proliferating cells (6,11).

Because of its longer half-life (12), 18F-labeled choline is more suitable for routine clinical use than 11C-labeled. At present, 18F-fluoromethylcholine is used mainly for restaging of PCa in case of biochemical relapse. As uptake of 18F-fluoromethylcholine should reflect viable tumor tissue, changes over time may serve as a measure of response to therapy. For monitoring response to systemic treatment in metastasized PCa, however, accurate quantification is required.

To date, 18F-fluoromethylcholine biodistribution has been assessed with encouraging results (13-16), but full kinetic analysis has not yet been reported. In the present study, pharmacokinetic modeling of dynamic PET data in combination with arterial blood sampling was used to determine
the appropriate plasma input compartment model for $^{18}$F-fluoromethylcholine. In addition, the validity of using an image derived input function in combination with manual venous blood samples instead of arterial blood sampling was investigated and the validity of using simplified methods for quantification of $^{18}$F-fluoromethylcholine was assessed.

MATERIALS AND METHODS

Eight patients with histologically proven prostate cancer with lymphatic and/or haematogeneous metastases were included. Inclusion criteria were presence of at least 2 metastases (diameter $\geq 1.5$cm) and ability to remain supine for 50min. Exclusion criteria were claustrophobia, multiple malignancies and anticoagulant therapy. The study was approved by the Medical Ethics Review Committee of the VU University Medical Center. Prior to inclusion, each patient signed a written informed consent after receiving verbal and written explanation.

Synthesis Of $^{18}$F-fluoromethylcholine

$^{18}$F-fluoromethylcholine was synthesized according to the methods proposed by DeGrado et al. (6) with minor modifications and by use of automated modules (17). Details are given in Supplemental data 1.

Data Acquisition

Each patient received a lowdose CT (50mAs, 120kVp) followed by a 40min dynamic PET scan with the field of view (FOV) centered over the largest metastases (abdominal region: N=5; lung area: N=3), on a Gemini TF-64 PET/CT (Philips Medical Systems, Cleveland, Ohio, USA). At the start of the PET scan a bolus injection of approximately 204±9MBq $^{18}$F-fluoromethylcholine (specific activity 94.9±65.7GBq·µmol$^{-1}$) was administered intravenously using an automated
injector (Medrad, Pittsburgh, USA) and flushed with 40mL of saline (5mL at 0.8mL·s⁻¹ followed by 35mL at 2mL·s⁻¹). PET data were normalized and corrected for attenuation, dead time, randoms, scatter and decay, and reconstructed into 34 frames (1x10s, 8x5s, 4x10s, 3x20s, 5x30s, 5x60s, 4x150s, 4x300s) with a matrix size of 144x144x45 voxels (4x4x4mm³) using a 3-dimensional row action maximum likelihood reconstruction algorithm (3D-RAMLA) (18).

Arterial blood activity concentration over time was determined by continuous arterial blood sampling (5mL·min⁻¹ for 5min, 2.0mL·min⁻¹ thereafter) using an automated blood sampling device (19) connected to a cannula inserted into the radial artery. At 6 time points (5, 10, 15, 20, 30 and 40min p.i.) manual arterial blood samples were collected, whilst briefly pausing blood sampler operation. In addition, manual venous blood samples were collected at 5, 15 and 30min p.i. Following each sample, the cannula was flushed with heparinized saline to prevent clotting. Each manual sample was analyzed for whole-blood activity concentration, plasma-to-whole blood ratio and presence of radiolabeled metabolites in plasma. Following plasma protein extraction, metabolite analysis was performed on the remaining plasma (extraction efficiency of 88%) using a method based on Sutinem et al. (11) involving high performance liquid chromatography.

Kinetic Analysis

In pharmacokinetic modeling, tracer kinetics are assumed to be separable into compartments that are connected in series to the arterial blood compartment, represented by the plasma input function, by (transport) rate constants. For example, in the irreversible two-tissue compartment model (2T3k) the first compartment often represents tracer free in tissue while the second represents irreversible specific uptake. From the rate constants connecting the compartments, the net influx rate for the second compartment can be calculated: \( K_{i} = K_{i} / (k_{2} + k_{3}) \). See Supplemental data 2 for more details on each of the models and associated quantification parameters.
Metabolite corrected blood sampler plasma input functions (BSIF) were derived from blood sampler data (corrected for intermittent reductions in counts associated with saline flushes), calibrated using whole-blood activity concentrations measured from manual arterial blood samples. In addition, data were multiplied by the plasma-to-blood ratio curves and parent fraction curves derived from manual arterial blood samples using a single exponential fit and Watabe fit \((20)\), respectively, and corrected for delay \((21)\). Metabolite corrected image derived plasma input functions (IDIF) were derived from volumes of interest (VOI; \(2.85\pm1.65\)mL; range: \(0.64-5.89\)mL) defined manually on an early PET frame most clearly displaying the blood pool (Fig. 1A), within the largest arterial blood pool structures available (left ventricle or aortic, femoral or iliac arteries). These VOI were then projected onto the dynamic PET scan to derive time activity curves (TAC), which were processed in the same fashion as BSIF.

Tissue TAC were derived from several tissue VOI. Lesion VOI were defined using a 50% threshold technique with background correction, in all metastatic lymph nodes that were clearly visible on the averaged PET image over 25-40min p.i. (24 in total; \(4.76\pm3.54\)mL; range: \(0.7-12.8\)mL). Healthy tissue VOI were manually defined using the lowdose CT (muscle, fat, liver).

Several standard compartment models were then fitted to the lesion TAC using standard non-linear regression analysis (NLR) routines \((22)\), with both BSIF or IDIF as input functions. Models evaluated were the general irreversible and reversible single-tissue compartment models \((1T1k\) and \(1T2k,\) respectively) and the irreversible and reversible two-tissue compartment models \((2T3k\) and \(2T4k,\) respectively). To account for contribution from blood activity to the tissue TAC, performance of all models was evaluated with and without blood volume parameter \((V_B)\).

Boundary conditions for all estimated kinetic parameters were determined after multiple runs \((K_1:\ [0,3], k_2:\ [0,2], k_3/k_4:\ [0,10] \) and \(V_B:\ [0,1])\). Fits with low precision (as indicated by SE>500% in at least one of the estimated rate constants) were considered unsuccessful and excluded from further
analysis. Robustness of the model was evaluated as the percentage of successfully fitted lesion TAC.

**Validation**

*Model Selection* Selection of the model providing the best fits to the lesion TAC was based on the Akaike Information Criterion (AIC) for small sample sizes (23) as well as on model robustness. In clinical practice, lengthy (dynamic) scanning procedures are less attractive. Therefore, the minimal scan duration required to derive accurate results was assessed by comparing relevant uptake parameters resulting from kinetic modeling of parts of the dynamic scan (0-5min, 0-10min, 0-15min, 0-20min, 0-25min or 0-30min p.i.) with those of the full dynamic scan (0-40min p.i.).

*Alternatives To Arterial Blood Sampling* Deriving an accurate plasma input function requires insertion of an arterial cannula, automated blood sampling and specialist metabolite analysis. As these methods may not be feasible in a routine clinical setting, the validity of using IDIF instead of BSIF as well as the need for manual arterial or venous blood samples, were assessed.

*Simplified Methods* Once validated, simplified methods can provide estimates of relevant uptake parameters using a far simpler imaging protocol than that required for full kinetic modeling. Therefore, performance of several simplified measures was evaluated, e.g. lesion-to-muscle ratio (LMr), lesion-to-blood ratio (LBr) and standardized uptake value (SUV) for several normalization factors: body weight (BW), body surface area (BSA), lean body mass (LBM), body mass index (BMI) and ideal body weight (IBW).
RESULTS

Eight patients diagnosed with PCa were included: age 66±8y, weight 89±12kg, height 185±7cm, T-stage≥2, Gleason score 7 (N=2) or 9 (N=6) and high PSA at the time of PET/CT imaging (113±91ng/ml). Patients were previously treated by prostatectomy (N=4) or external beam radiotherapy on the prostate in combination with anti-hormonal therapy (N=4). Three patients were receiving therapy at the time of PET/CT imaging: luteinizing hormone-releasing hormone (LHRH) antagonists, oral androgen receptor inhibitor Enzalutamide and dendritic cell therapy, respectively. Fig. 1 shows typical 18F-fluoromethylecholine PET/CT images. Two typical examples of acquired blood activity concentrations are shown in Fig. 2.

Validation

Model Selection Typical tissue TAC are shown in Fig. 3A. Fig. 3B shows the same lesion TAC with associated NLR fits. AIC results indicate irreversible kinetics, with 2T3k+V_B producing the best fits (preferred model in 7/24 lesion TAC), followed by the simpler irreversible model 2T3k (7/24) and 1T1k+V_B (5/24). However, as displayed in Table 1, 2T3k+V_B was less robust than 1T1k+V_B while correspondence between respective quantification parameters was excellent (R²=0.96; ICC=0.94; Table 2) and remained so even for K_i derived from shorter scan durations (R²>0.92; ICC>0.89; SE[K_i<5%]; for scan durations >20min). It is therefore conceivable that K_i can be substituted by K_1 produced by the 1T1k+V_B model without loss of accuracy. Therefore, in the validation analysis presented in this paper, K_1 produced by full kinetic modeling with 1T1k+V_B for the 40min dynamic PET scan will be used as reference. One patient was excluded as for this patient estimated K_1 values were outside of the expected physiological range (see “Discussion”). For sake of completeness, Supplemental data 3 shows results for 2T3k+V_B.
Alternatives To Arterial Blood Sampling  IDIFs overestimate whole-blood activity concentrations at later time points compared to BSIF (as illustrated in Fig. 2), most markedly when derived from VOI located near high $^{18}$F-fluoromethylcholine uptake structures, such as the liver (Fig. 2B) or kidneys. Fig. 4 shows NLR results using IDIF derived from VOI in blood structures located away from the liver or kidneys only, compared with those using BSIF. To minimize calibration errors due to possible overestimation at late time points, calibration in IDIF was performed at approximately 500-1500s p.i. For one patient, imaged over the abdominal region, no suitable IDIF could be found as marked overestimation of blood activity concentrations was observed all along the descending aorta. Good correlation was found for calibrated IDIF (calibration factor 0.82±0.13), although a bias was observed ($R^2=0.83$, slope=1.19; ICC=0.74). Fig. 4B shows results for non-calibrated IDIF ($R^2=0.72$; ICC=0.80). Input function correction based on venous blood samples was not equivalent to correction based on arterial blood samples. Although good correspondence was found for whole-blood activity concentrations at late time points, and for plasma-to-blood ratios (ICC=0.89; Supplemental data 4), parent fraction measures were substantially different (ICC=0.61; Fig. 5).

Simplified Methods  Correlation between SUV (35-40min p.i.) en $K_1$ was poor (Table 3; Fig. 6A) with $R^2<0.34$, irrespective of the normalization factor used. LMr (35-40min p.i.; Fig. 6B) and LBr (35-40 min p.i) performed somewhat better ($R^2=0.50$ and $R^2=0.44$, respectively).

In contrast, $SUV_{AUC,PP}$, calculated by dividing lesion activity concentrations (35-40min p.i.) by cumulative delivery, i.e. the area under curve (AUC) of the parent plasma input function (0-40min p.i.), provided an excellent correlation to $K_1$ ($R^2=0.92$). This correlation reduced to $R^2=0.65$ for whole-blood AUC rather than parent plasma AUC ($SUV_{AUC,WP}$). $SUV_{AUC}$ calculated from lesion activity concentrations at 30-40min p.i. and AUC over 0-30min p.i. resulted in similar correlations: $R^2=0.91$ for $SUV_{AUC,PP}$ (Fig. 6C) and $R^2=0.64$ for $SUV_{AUC,WP}$ (Fig. 6D), respectively.
Good correspondence was found between SUV\textsubscript{AUC} derived from BSIF and SUV\textsubscript{AUC} derived from IDIF (calibrated: $R^2=0.98$; ICC=0.93; non-calibrated: $R^2=0.86$; ICC=0.91).

**DISCUSSION**

This study focused on pharmacokinetic analysis of $^{18}$F-fluoromethylcholine in PCa metastases and investigated the validity of strategies to simplify acquisition and analysis, to enable quantification of $^{18}$F-fluoromethylcholine uptake in a routine clinical setting.

Based on AIC alone, $^{18}$F-fluoromethylcholine kinetics in PCa lymph node metastases could best be described using a 2T3k+$V_B$ model. However, the fitting procedure proved non-robust, particularly for shorter scan durations (as shown in Table 1). We hypothesize this is caused by the rapid uptake in combination with limited efflux to the blood pool $(k_2)$, rendering the model unable to accurately distinguish $K_1$ and $k_3$. This also explains why 1T1k+$V_B$ yielded similar results ($R^2=0.96$; ICC=0.94). This indicates that, even though AIC indicated 2T3k+$V_B$, 1T1k+$V_B$ can be used without loss of quantification accuracy. Moreover, 1T1k+$V_B$ results were more robust and consistent for shorter scan durations, indicating this to be the most suitable model.

An additional issue arising from the fast kinetics observed for $^{18}$F-fluoromethylcholine is inability of either model to accurately distinguish between the first tissue compartment (influx $K_1$ and efflux $k_2$) and signal originating from blood volume in the VOI. High $V_B$ areas were therefore excluded.

One patient was excluded as $K_1$ estimates were found to be unrealistically high ($K_1>1$) using either irreversible model. We hypothesize this may be the result of high lesion blood volume fraction; despite our efforts to exclude large blood volume structures, as described previously, $V_B$ estimates were $0.49\pm0.05$. As rapid lesion uptake occurs, delayed arrival of blood activity concentrations in blood pool structures may have rendered them visually indistinguishable from lesion tissue.
Another explanation may be markedly different kinetics in this patient, leading to inaccurate estimates caused by using the wrong model. We were unable to verify or reject either hypothesis based on the available data. Interestingly, all lesions were located within the mediastinum. In the rest of the study population, 3 out of 4 mediastinal lesions also showed increased $V_B$ estimates ($0.23\pm0.11$ compared to $0.08\pm0.05$ for all other lesions studied). Also of interest is that this particular patient had received an experimental type of therapy (dendritic cell therapy; up to 1 month prior to the PET/CT scan). As many patients eligible for $^{18}$F-fluoromethylcholine PET will receive some form of therapy, possible influence of drugs on $^{18}$F-fluoromethylcholine kinetics should be investigated. For example, it has been suggested that androgen deprivation therapy (ADT), a pharmaceutical used to maintain the biochemical castration level in recurrent PCa, causes decreased choline uptake in hormone-sensitive PCa in various studies (24). In the present study, one patient was on ADT during the scan. Nevertheless, results were consistent with the rest of the study population, indicating negligible influence on $^{18}$F-fluoromethylcholine uptake for this patient.

Having determined the kinetic model and relevant quantification parameter, the possibilities for simplifying the acquisition protocol and analysis methods were investigated, i.e. alternatives for deriving plasma input functions as well as the validity of using simplified methods for quantification.

For several blood VOI locations, overestimation of blood activity concentrations was observed (for this reason one patient could not be analyzed with IDIF). We hypothesize that the apparent increase in image-derived blood activity concentrations near high $^{18}$F-fluoromethylcholine uptake structures is caused by incorrect scatter correction in these areas. This could lead to large quantification errors with IDIF derived from blood VOI in these areas. For other blood VOI,
however, good correspondence was found for results with IDIF and BSIF ($R^2=0.83$ and ICC=0.74 for calibrated IDIF). The observed 19% bias was mainly caused by results for IDIF originating from small (femoral) arteries (Fig. 4), indicating that these may not be suitable for deriving IDIF. Concluding, IDIF derived from large blood pool structures located away from high-uptake structures, such as the aortic arch, can substitute continuous arterial blood sampling. Unfortunately, manual arterial blood samples and specialized lab analysis remain necessary as parent fractions are greatly reduced shortly after injection and variability between patients is high (12±4% at 20min. p.i.; Fig. 5). Parent fractions measured from venous blood showed low correspondence to those obtained from arterial blood samples.

High metabolite formation rates may also complicate quantification when radiolabeled metabolites enter tissue. Main metabolite is betaine, an organic osmolyte (10). As presence of $^{18}$F-betaine will not be specific to lesions and LMr as high as 7.84±3.15 were observed (Fig. 6B), it is unlikely that radiolabeled betaine significantly affected observed lesion activity concentrations.

A major simplification of the imaging protocol would be to use simplified methods instead of full kinetic modeling. Simplified methods, such as SUV, however, do not take into account possible influences on quantification by $V_b$, metabolite formation, etc. Therefore, results obtained using simplified methods were compared to those obtained with full kinetic modeling. Commonly used simplified methods showed poor correlation to results from full kinetic modeling (SUV: $R^2<0.34$, LMr: $R^2=0.50$; LBr: $R^2=0.44$). We hypothesize that as $^{18}$F-fluoromethylcholine kinetics is very rapid and irreversible, even late-time lesion activity concentrations will depend heavily on the AUC of the plasma input function, a characteristic not accounted for in commonly used simplified methods. $SUV_{AUC}$ performs better since it incorporates information from the input function itself ($R^2=0.92$ for $SUV_{AUC,pp}$ and $R^2=0.65$ for $SUV_{AUC,wb}$).
In a routine clinical setting, static imaging would be preferable. Whole-blood AUC can be image-derived directly from a static PET image acquired over 0-40min p.i. \((R^2=0.98)\), from a VOI within the aortic arch defined using the low dose CT. However, simultaneous imaging of both the lesions and the aortic arch will be impossible in the majority of patients, as the typical metastatic pattern of PCa usually involves the pelvic or abdominal region. Therefore, \(SUV_{AUC}\) was also validated when obtained from two consecutive time intervals: AUC over 0-30min p.i. and lesion activity concentrations averaged over 30-40min p.i. \((R^2=0.91\) for metabolite-corrected plasma data, \(R^2=0.64\) for whole-blood data). As lesion activity concentrations appear stable from 10min onwards, the latter can also be obtained with a whole-body PET scan. To obtain \(SUV_{AUC,PP}\) arterial blood sampling and analysis would be required. It should also be noted that with the proposed static imaging protocol VOI cannot be adjusted to exclude high \(V_B\) areas as for this an early PET image over the lesion is required. Apart from aforementioned modeling issues, high \(V_B\) causes underestimation in simplified parameters. We therefore recommend caution when evaluating lesions near arterial structures until the clinical impact of these potential errors has been fully investigated.

Characteristics such as metabolism, perfusion and blood volume fraction are likely to change over the course of therapy. Therefore, the performance of the parameters presented in this paper should be verified in test-retest and longitudinal trials, before they can be validated or disqualified for application in a clinical (response monitoring) setting. Should \(^{18}\text{F}\)-fluoromethylcholine metabolism remain constant throughout the response monitoring study, performance of \(SUV_{AUC,WB}\) and to a lesser extent SUV may be equivalent to \(SUV_{AUC,PP}\) as a relative measure of response. Challapalli et al. recently reported on a novel \(^{18}\text{F}\)-labeled choline tracer that metabolizes less rapidly than \(^{18}\text{F}\)-fluoromethylcholine, with parent fractions gradually decreasing to approximately 0.3 over the first
hour p.i. (25,26). With decreased inter-patient variability in parent fractions, performance of SUV and SUV_{AUC,WB} may improve with respect to SUV_{AUC,PP}.

**CONCLUSION**

$^{18}$F-fluoromethylcholine uptake should be quantified using full kinetic modeling with 1T1k+$V_B$ and metabolite-corrected plasma input function based on arterial blood sampling.

Results indicate that SUV cannot be used to estimate $^{18}$F-fluoromethylcholine uptake. A clinically feasible alternative could be SUV_{AUC,WB} based on two consecutive static PET scans. Further studies are needed to substantiate these findings.

**ACKNOWLEDGEMENTS**

The authors would like to thank our colleagues at the Department of Radiology & Nuclear Medicine involved in tracer production and data acquisition for this study. We are also grateful to the urologists from VUmc (Dr. André N. Vis), Amstelland Hospital Amstelveen (Dr. Cobi Reisman, Dr. Joop W. Noordzij) and Medical Center Alkmaar (Dr. Ton A. Roeleveld) as well as the VUmc oncologists (Dr. Jens Voortman, Dr. Marije M. Vleugel, Dr. Liselot Wertenbroek, Dr. Maurice J.D.L.van der Vorst) for their contribution to patient selection and inclusion.

**CONFLICT OF INTEREST**

The authors declare that they have no conflict of interest.
REFERENCES


FIGURE 1. Typical example of PET/CT images acquired from a patient diagnosed with PCa. Shown are the low dose CT (grey scale) fused with (a) an early PET image acquired from 35-40s p.i. displaying the blood pool, and (b) an averaged image over 25-40min after $^{18}$F-fluoromethylcholine injection (color).
FIGURE 2. Two typical examples of measured whole-blood time activity curves for (A) a patient imaged over the thorax and (B) a patient imaged over the abdominal region. Lines represent calibrated blood sampler data, dashed lines (image derived) aortic arch, dash-dot lines (image derived) abdominal descending aorta, triangles manual arterial blood samples and squares manual venous blood samples.
FIGURE 3. (A) Typical measured time activity curves (TAC) for the patient shown in Fig. 1. Square represents liver, circle lesion, diamond muscle and triangle fat tissue. (B) Non-linear regression fits to the lesion TAC displayed in A, using various compartment models.
FIGURE 4. $K_1$ obtained using $1T1k+V_B$ with (A) calibrated and (B) non-calibrated IDIF derived compared with BSIF. Symbols indicate IDIF origin: triangle aortic arch, square descending aorta, plus femoral artery.
FIGURE 5. Manual blood sample data as function of time: (A) mean parent fractions (triangle arterial, square venous) and (B) ratio of venous to arterial parent fractions. Error bars represent ±1SD.
FIGURE 6. Correlation between simplified uptake measures and $K_1 (1T1k+V_b)$. (A) standard uptake value normalized to body weight (SUV$_{BW}$), (B) lesion-to-muscle ratio (LMr) and lesion activity concentration in kBq at 30-40min p.i. divided by AUC of (C) parent plasma and (D) whole-blood activity concentration in MBq over 0-30min (SUV$_{AUC,PP}$ and SUV$_{AUC,WB}$, respectively).
### Tables

**Table 1.** Comparing scan durations.

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<th>Parameter (model)</th>
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<th>Robustness (%)</th>
<th>Linear regression analysis</th>
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* Results for comparison of quantification parameters from short scan durations to those derived from the full 40 min dynamic scan.
Table 2. Comparing 1T1k+V_B to 2T3k+V_B.

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* Comparison of K_i derived with 1T1k+V_B for various scan durations to K_i derived with 2T3k+V_B from the full 40 min dynamic scan.
Table 3. Comparison of simplified parameters to $K_1$ resulting from full kinetic modeling with $1T1k+V_B$.

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