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Original research

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Posted Date: September 25th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-82216/v1>

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***Estimation of renal perfusion based on measurement of Rubidium-82
clearance by PET/CT scanning in healthy subjects***

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Abstract

Background: Changes in renal blood flow (RBF) may play a pathophysiological role in hypertension and kidney disease. However, RBF determination in humans has proven difficult. We aimed to confirm the feasibility of RBF estimation based on positron emission tomography/computed tomography (PET/CT) and rubidium-82 (^{82}Rb) using the abdominal aorta as input function in a 1-tissue compartment model.

Methods: Eighteen healthy subjects underwent two dynamic ^{82}Rb PET/CT scans in two different fields of view (FOV). FOV-A included the left ventricular blood pool (LVBP), the abdominal aorta (AA) and the majority of the kidneys. FOV-B included AA and the kidneys in their entirety. In FOV-A, an input function was derived from LVBP and from AA; in FOV-B from AA. 1-tissue compartmental modeling was performed using tissue time activity curves generated from volumes of interest contouring the kidneys, where the renal clearance of ^{82}Rb is represented by the K_1 kinetic parameter. To investigate the correct interpretation of K_1 , we assumed to first estimate effective renal plasma flow (ERPF) by extrapolating clearance values ($\text{ml}/\text{min}/\text{cm}^3$) to whole kidney values (ml/min) using the estimated total kidney volume. Thereafter, RPF was estimated from ERPF using an assumed extraction fraction (0.89). Lastly, RBF was estimated from RPF using measured haematocrit values. Intra-assay coefficients of variation and inter-observer variation were calculated.

Results: For both kidneys, K_1 values derived from AA did not differ significantly from values obtained from LVBP, neither were significant differences seen between AA in FOV-A and AA in FOV-B, nor between the right and left kidneys. For both kidneys, the intra-assay coefficients of variation were low ($\sim 5\%$) for both input functions. The measured K_1 of $2.04 \text{ ml}/\text{min}/\text{cm}^3$ suggests an estimated total renal perfusion normalized to body surface area of $628 \pm 95 \text{ ml}/\text{min}/1.73 \text{ m}^2$ and subsequently an estimated RBF of $1091 \pm 162 \text{ ml}/\text{min}/1.73 \text{ m}^2$.

1 Conclusion: RBF estimation based on PET/CT and ^{82}Rb using AA as input function in a 1-tissue
2 compartment model is feasible in a single FOV. The measured K_1 clearance values are most likely
3 representative of ERPF rather than estimated RBF values.

4 **Keywords:**

5 PET/CT, Rubidium-82, Pharmacokinetic modelling, Renal blood flow, Effective renal plasma flow

6 **Background**

7 Kidney disease and hypertension are major contributors to the overall global disease burden. In the
8 pathogenesis of acute kidney injury (AKI), renal ischemia, as a result of a reduction in total RBF,
9 has been accepted as a significant factor. However, recent studies suggest that renal hypoperfusion
10 may play a less important role (1, 2). In fact, RBF measurements in sepsis-associated AKI have
11 shown much discrepancy; reduced, normal, or even increased RBF have been reported (3-5). In
12 patients with chronic kidney disease (CKD), RBF is reduced compared with controls (6, 7),
13 possibly contributing to the progression of renal dysfunction. In renal circulation studies, most
14 patients with essential hypertension display reduced RBF (8, 9); the greatest reduction demonstrated
15 in malignant hypertension (9, 10). Additionally, renal vasoconstriction has been identified in pre-
16 hypertensive adults, indicating that renal vascular abnormalities could be a cause of hypertension
17 rather than caused by hypertension (11, 12).

18 Quantification of renal perfusion in humans has proven difficult. Current clearance-based methods
19 estimating ERPF are time consuming and burdensome for patients (13-15) and alternative
20 radiological imaging techniques assessing RBF, such as magnetic resonance imaging and
21 ultrasonography, all have considerable limitations (7, 16) – none of which have been routinely
22 implemented in clinical practise. Dynamic positron emission tomography (PET) using perfusion
23 tracers is currently considered the most accurate, non-invasive method for determination of organ

1 perfusion. Thus, with good homogeneity and high perfusion rate, the kidneys are well suited for
2 PET studies.

3 PET scans using ^{82}Rb are routinely performed to assess myocardial blood flow in patients suspected
4 of ischemic heart disease (17, 18). ^{82}Rb is a potassium analogue with a short half-life of 75 seconds,
5 produced in a generator by the radioactive decay of strontium-82 (^{82}Sr). Due to its high first-pass
6 renal extraction (~ 90%) and slow wash-out, ^{82}Rb is well suited for mathematic modelling of RBF
7 using dynamic PET-methods (19).

8 The first human ^{82}Rb PET/CT study of renal perfusion showed high image quality, resolution and
9 contrast, as well as demonstrated a high natural ^{82}Rb renal uptake (20, 21). RBF was evaluated
10 using a 1-tissue compartment model, where the K_1 parameter is presumed to represent estimated
11 RBF.

12 Compartmental modelling requires an input function (IF) described by a blood-pool time activity
13 curve (TAC). In quantification of myocardial blood flow, the LVBP has been validated as an
14 image-derived input function (IDIF) (22, 23), obviating the need for arterial blood sampling.

15 However, the LVBP is not necessarily ideal for studying renal perfusion, as the LVBP and the
16 kidneys in their entirety may not fit within a single limited axial scanner-FOV. This is especially
17 true for older PET-scanners. In order, to ensure that an IF is estimated as correctly as possible, as
18 well as to minimize radiation dose associated with the scanning, inclusion of the blood-pool and the
19 kidneys in their entirety in the same FOV, is important. This can be accomplished if the AA can
20 replace the LVBP as IF in the model, as suggested by Tahari et al. (21).

21 To determine whether this method is suitable for clinical, reliable assessment of RBF, this study
22 further explores the substitution of AA as a valid alternative to LVBP by comparing the resulting K_1
23 values obtained from use of the two different IFs. Method precision was evaluated by determination
24 of intra-assay coefficients of variation for both IFs. Furthermore, current literature assumes that the
25 perfusion quantity measured using ^{82}Rb is estimated RBF. Early investigations into the exchange

1 rates of radioactive potassium and rubidium between plasma and erythrocytes showed rates of ~ 2%
2 per hour (24, 25), implying that initially, and hence during renal uptake studies, the majority of
3 injected ^{82}Rb will be almost exclusively present in plasma. We discuss and question whether flow
4 values measured by ^{82}Rb clearance are actually representative of RBF, or whether they should be
5 interpreted as estimates of ERPF.

6 **Methods**

7 **Study design**

8 This study was performed as a randomized cross-over study (Fig. 1). During a period of
9 approximately 45 minutes, each subject underwent four 8-minute dynamic ^{82}Rb PET/CT scans in
10 two different bed positions, A and B (FOV-A and FOV-B). In each bed position, duplicate scans
11 were performed.

12 **Participants**

13 Healthy participants were recruited through advertisement, primarily at local educational
14 institutions. Prior to inclusion, each participant completed a screening program. Screening consisted
15 of a medical history; a clinical examination including measurements of weight, height, and blood
16 pressure; electrocardiography as well as blood tests to determine electrolytes, creatinine, albumin,
17 alanine aminotransferase (ALAT), leucocytes, haemoglobin, haematocrit and thrombocytes. Urine
18 was screened for leucocytes, glucose, nitrite, ketones, and haemoglobin. In female subjects,
19 pregnancy was ruled out. Inclusion criteria were: men and women aged 18-40 years with a body
20 mass index (BMI) in the range 18.5-30.0 kg/m². Exclusion criteria were: medical treatment (except
21 hormonal contraceptives); pregnancy or breastfeeding; smoking; substance abuse; alcohol
22 consumption >14 units¹ per week for men and >7 units per week for women; signs of clinically
23 relevant kidney disease, heart disease, liver disease or endocrine disease in the history, clinical

¹ Danish alcohol unit = 15 ml (12 g) pure alcohol.

1 examination, or the paraclinical tests; hypertension; neoplastic disease, and blood donation within 1
2 month of the examination day. Withdrawal criteria were development of exclusion criteria or
3 withdrawal of consent.

4 **Number of subjects**

5 17 subjects are required to detect a 0.40 ml/min/cm^3 difference in RBF (standard deviation (SD)
6 0.38 ml/min/cm^3) for a 5% significance level and power of 80%. To allow for dropout, 20 subjects
7 were included.

8 **Pre-scan procedure**

9 For 24 hours preceding the acquisition of PET/CT scans, fluid intake was standardized to 35 ml/kg
10 body weight of still water, subjects maintained a free diet and were instructed to avoid strenuous
11 exercise. Subjects arrived at 8 a.m. at the Department of Nuclear Medicine, Herning Hospital,
12 Regional Hospital West Jutland, Denmark after an overnight fast. In female subjects, pregnancy
13 was ruled out.

14 **Radiopharmaceutical**

15 On each day of examination, the $^{82}\text{Sr}/^{82}\text{Rb}$ generator (Cardiogen-82; Bracco Diagnostics Inc.,
16 Monroe Township, NJ, USA) was quality checked according to approved guidelines (Bracco
17 Diagnostics Inc.) including test for breakthrough of $^{82}\text{Sr}/^{85}\text{Sr}$. The generator was calibrated to
18 deliver a dose of 555 MBq (15 mCi) ^{82}Rb for each injection. ^{82}Rb was administered as a bolus-
19 injection using a pre-programmed pump and infusion system. The subjects received four doses in
20 total.

21 **PET/CT scanning**

22 All PET/CT scans were performed on the same scanner (Siemens Biograph mCT; 64 slice-4R) with
23 a 22 cm axial FOV. On each day of examination, the PET/CT scanner was quality checked and

1 calibrated according to system required procedures. A peripheral venous catheter (Venflon) was
2 placed in a cubital vein for ^{82}Rb injection. Subjects rested in a sitting position for approximately 30
3 minutes before voiding. They were then placed in a supine position in the PET/CT scanner with
4 arms extended above the head and the generator infusion system connected to the Venflon. All
5 subjects underwent two consecutive duplicate PET/CT scans. The duplicate scans were acquired in
6 bed position A (FOV A), including the LVBP, the AA and as much of the kidneys as possible (Fig.
7 2a) and bed position B (FOV B), including the AA and the kidneys in their entirety (Fig. 2b).
8 Computer generated randomization determined the acquisition sequence for the two FOVs for each
9 participant. In each bed position, an initial planar scout image was acquired to determine
10 positioning of the scanner over the required FOV. Following positioning, a low-dose CT scan was
11 performed immediately followed by a bolus injection of 555 MBq ^{82}Rb and a dynamic PET-scan in
12 list-mode for 8 minutes synchronized with the start of injection (21). Sequentially, and 10 minutes
13 after the first PET scan was initiated, a second dose of ^{82}Rb was administered and a duplicate PET
14 scan performed in list-mode for 8 minutes. The bed position was then shifted, and the procedure
15 repeated for the second FOV.

16 Low-dose CT scans (25 mAs, 100 kV) were performed for attenuation correction purposes only.
17 PET data were acquired in dynamic list-mode, which was re-binned using 32 frames (20×6 s, 5×12
18 s, 4×30 s and 3×60 s) and iteratively reconstructed (21 subsets, 2 iterations) using Siemens TrueX
19 and time-of-flight reconstruction in a matrix of 128×128 (voxel size: 6.4 x 6.4 x 3.0 mm³) and post-
20 filtered with a 5.0 mm Gaussian filter to produce attenuation and decay corrected dynamic
21 sequences. We found it unnecessary to correct for motion of the kidneys.

22 The effective radiation dose associated with the study was < 4 millisievert (mSv): each low-dose
23 CT scan contributed 0.4 mSv and each 555 MBq bolus injection of ^{82}Rb contributed with 1.26
24 μSv/MBq (20).

1 Analysis of ⁸²Rb PET/CT studies

2 A 1-tissue compartment model was used for flow estimation (21), as illustrated in Fig. 3. The K_1
3 parameter represents the renal clearance of ⁸²Rb, where K_1 (ml/min/cm³) is equal to the product of
4 the blood flow component carrying the ⁸²Rb (erythrocyte and/or plasma) and its extraction fraction
5 (EF) in the kidneys. Due to ⁸²Rb having a high first pass extraction (~ 90%) (19), its uptake rate K_1
6 will be closely related to, and hence can be used as, an estimate of flow (26). Compartmental
7 modelling was performed using the PMOD software (PMOD Technologies Ltd., Zurich,
8 Switzerland, version 4.01).

9 TACs were obtained by defining relevant volumes of interest (VOIs) in the various anatomical
10 regions-of-interest (Fig. 4), with the LVBP and AA defining IFs for the kinetic modelling. The
11 LVBP was defined in FOV-A using a limiting box and the hot-contour tool with a typical cut-off 45
12 – 60% of the maximum limiting box activity. Ensuring avoidance of surrounding activity in the
13 right and left ventricular luminae, a background VOI was manually placed centrally in the left
14 ventricular wall and defined on at least 10 contiguous slices. Partial-volume effect (PVE) and spill-
15 over activity from the left ventricular wall was then corrected adopting the method described by
16 Katoh et al. (27).

17 The AA-VOI was defined in both FOVs using a box (10×10×30 mm³) placed in the lumen of the
18 abdominal aorta cranially to the departure of the renal arteries. An aortic background VOI was
19 defined within a limiting box around the AA-VOI by applying a cold-contour with typical cut-off
20 10 – 25% and excluding all structures not representing background activity.

21 Based on the formulation for PVE and spill-over of background activity correction in LVBP (27),
22 AA activity can be similarly corrected using:

$$23 \quad R_A(t) = \beta \cdot C_A(t) + (1 - \beta) \cdot Bg(t) \quad (\text{Eq. 1})$$

where $C_A(t)$ represents the corrected AA activity, $R_A(t)$ is the measured AA activity, $C_{Bg}(t)$ is the measured aortic background activity and β represents the recovery coefficient to be determined. To find the optimal β -value for AA activity curve correction, multiple choices for β in the range 0.5 – 1.0 were systematically tested with the optimal subject-specific β -value defined as the value resulting in the corrected AA peak-activity best approximating the β -corrected peak-activity for LVBP for each individual. The mean recovery coefficient was calculated as the average of all individually determined optimal β -values, after which the AA activity for each subject was corrected using both the subject-optimized β -value and the mean β -value.

Tissue-TACs for both kidneys were obtained using hot-contouring in both FOVs as described previously and K_1 values for each kidney obtained for both LVBP and AA IFs using the 1-tissue compartment model. A blood volume fraction of 10% was assumed to account for activity from the vascular space within the VOIs contouring the kidneys (28).

Kinetic analysis was performed independently by two observers; a medical resident (observer 1) and an experienced nuclear medical physician (observer 2).

Renal blood flow estimation

Assuming that, after intravenous injection and throughout the 8-minute duration of the study acquisition ^{82}Rb is almost exclusively distributed in the plasma [24, 25], then ERPF can be estimated using the measured ^{82}Rb clearance (K_1) and the total kidney volume (V_{Total}) as determined by the renal contour volumes described above:

$$ERPF = K_1 \cdot V_{\text{Total}} \quad (\text{Eq. 2})$$

RPF can be estimated using the assumed EF (~ 0.89 [19]):

$$RPF = \frac{ERPF}{EF} \quad (\text{Eq. 3})$$

Subsequently, estimated RBF can be calculated from estimated RPF using the haematocrit (Hct) as:

$$RBF = \frac{RPF}{1-Hct} \quad (\text{Eq. 4})$$

Results for estimated RPF and RBF are normalized to body surface area (BSA) using the Dubois formula:

$$BSA = 0.007184 \cdot height^{0.725} \cdot weight^{0.425} \quad (\text{Eq. 5})$$

Statistical analysis

Statistical tests were performed using SPSS Statistics ver. 20 (IBM Corp., Armonk, NY, USA). For each subject, the result for K_1 was defined as the mean value of the two independent K_1 values determined for each FOV for both input functions.

Values are presented as mean $\pm$ SD for all completing subjects. Paired sample t-testing was used for comparison of K_1 values obtained using LVBP and AA IFs, where $p < 0.05$ was considered statistically significant.

Intra-assay coefficients of variation were calculated for each kidney based on the duplicate K_1 determinations in each FOV. Inter-observer variability was assessed using the intra-class correlation coefficient (ICC) with 95% confidence interval (CI) (29).

Results

Demographics

The participation flow chart for the study is depicted in Fig. 5. Eighteen healthy subjects completed the study and had scans accepted for analysis. Clinical and biochemical characteristics are shown in Table 1.

1 **Table 1** Clinical and biochemical characteristics (n=18)

Age (years)	21 ± 4
Gender (women/men)	7/11
BMI (kg/m ²)	24.1 ± 2.5
Office SBP (mmHg)	127 ± 9
Office DBP (mmHg)	73 ± 10
Heart rate (beats/min)	71 ± 11
P-alanine aminotransferase (U/L)	26 ± 11
P-sodium (mmol/L)	140 ± 2
P-potassium (mmol/L)	3.7 ± 0.2
P-albumin (g/L)	43 ± 3
P-creatinine (μmol/L)	73 ± 13
eGFR _{MDRD} (mL/min/1.73m ²)	118 ± 11
B-hemoglobin (mmol/L)	9.0 ± 0.4
B-leucocytes (x 10 ⁹ /L)	7.1 ± 1.9
B-thrombocytes (x 10 ⁹ /L)	275 ± 48
B-haematocrit	0.42 ± 0.02

2 Data are presented as mean ± SD. BMI, Body Mass Index; SBP, systolic blood pressure; DBT, diastolic blood pressure;
3 eGFR_{MDRD}, estimated glomerular filtration rate calculated using the Modification of diet in renal Disease Study
4 equation; EVF, erythrocyte volume fraction

5

6 **Recovery coefficient**

7 The optimal recovery coefficient for correction of PVE and spill-over in the AA varied for all
8 subjects with the mean optimal β -value = 0.69 ± 0.09 (range 0.53 – 0.80).

9 **Input curves**

10 Fig. 6 illustrates typical TACs generated from VOIs in the LVBP and the myocardium, as well as β -
11 corrected activity in LVBP. For all curves, the activity peaks rapidly. However, whereas for LVBP
12 the flow-peak is followed by a continuous decline, the myocardial activity plateaus around 1.0
13 minute post injection (p.i.) after the decline of the initial flow-peak.

14 Fig. 7 illustrates typical TACs generated from VOIs placed in the AA and the aortic background (β -
15 corrected as well as uncorrected), with β -corrected LVBP activity included for comparison. As for

1 LVBP, AA activities rapidly reach their maximum peak followed by rapid declines, while the aortic
2 background activity rises slowly until reaching a plateau between 0.5 and 3.0 minutes p.i. followed
3 by a slow decline.

4 Uncorrected AA activity reaches a substantially lower peak than LVBP activity. By definition, AA
5 activity corrected using the subject-specific recovery coefficient β and β -corrected LVBP activity,
6 reach similar peak maxima. For the shown subject, AA corrected activity using the mean β -value
7 reaches a higher peak than the measured LVBP activity.

8 Fig. 8 shows typical TACs generated from VOIs in the β -corrected LVBP activity, the AA
9 (corrected using the mean β -value) and within the kidney contours. The kidney uptake rises more
10 slowly until reaching a plateau between 1.5 and 4.5 minutes p.i. followed by a slow decline.

11 **Renal clearance - measurement of K_1 , estimation of ERPF and RBF**

12 High renal uptake of ^{82}Rb was demonstrated with no discernible urinary activity (Fig. 9).

13 The caudal part of the kidneys was outside FOV-A in 5 out of the 18 completing subjects.

14 Measurements in FOV-B showed that K_1 for the excluded caudal sections did not differ from the
15 global K_1 for the kidneys.

16 Table 2 presents the mean K_1 results for all IFs applied in the analysis. K_1 values using the
17 uncorrected AA IF were significantly higher than those using LVBP, whereas K_1 derived from
18 subject-specific β -corrected, and those from mean β -corrected AA IFs, were not significantly
19 different from LVBP values. No significant difference was observed between left and right kidneys.

20

21

22

Table 2 Mean K_1 values for all investigated input functions

	FOV-A				FOV-B	
	β -corrected LVBP	Uncorrected AA	β -corrected AA Subject- optimized β -value	β -corrected AA Mean β -value	Uncorrected AA	β -corrected AA Mean β -value
Right kidney	2.02 ± 0.31	2.91 ± 0.48^a	2.07 ± 0.28^{bc}	2.09 ± 0.35^{bcd}	2.86 ± 0.45^a	2.05 ± 0.33^{cef}
Left kidney	2.00 ± 0.31	2.88 ± 0.46^a	2.04 ± 0.28^{bc}	2.06 ± 0.33^{bcd}	2.84 ± 0.42^a	2.03 ± 0.30^{cef}

Data are presented as mean $\pm$ SD. K_1 units are ml/min/cm³. Paired t-test ^a: $p < 0.001$ vs. K_1 values derived from LVBP, ^b: $p < 0.001$ vs. K_1 values derived from uncorrected AA activity in FOV-A. ^c: NS vs. K_1 values obtained from LVBP. ^d: NS vs. K_1 values obtained from subject-specific β -corrected AA activity. ^e: $p < 0.001$ vs. K_1 values derived from uncorrected AA activity in FOV-B. ^f: NS vs. K_1 values obtained from corrected AA activity using mean recovery coefficient (mean β -value) in FOV-A. LVBP, left ventricular blood pool; AA, abdominal aorta; FOV-A, field of view A; FOV-B, field of view B. NS: Non-significant

Intra-assay coefficients of variation for the duplicate VOIs for each FOV were calculated for K_1 derived from LVBP and mean β -corrected AA IFs. As illustrated in Table 3, the intra-assay coefficients of variation were similar ($\sim 5\%$) for both IFs.

Table 3 Intra-assay coefficients of variation using β -corrected activity

	LVBP	AA (FOV-A) Mean β -value	AA (FOV-B) Mean β -value
Right kidney	5.3	4.5	4.7
Left kidney	5.3	4.2	4.5

Data are presented as percentages. LVBP, left ventricular blood pool; AA, abdominal aorta; FOV-A, field of view A; FOV-B, field of view B. AA are using the mean β -value as recovery coefficient.

Table 4 shows inter-observer variability when using LVBP and mean β -corrected AA IFs for the two FOVs. Using LVBP, ICC was indicative of moderate to excellent reliability for both kidneys. For AA in FOV-A, ICC was suggestive of excellent reliability for the right kidney and good to excellent reliability for the left kidney. For AA in FOV-B, ICC was indicative of excellent reliability for both kidneys.

1

2 **Table 4** Inter-observer variability using β -corrected activity

	LVBP	AA (FOV-A) Mean β -value	AA (FOV-B) Mean β -value
Right kidney	0.884 (0.717; 0.955)	0.965 (0.909; 0.987)	0.976 (0.936; 0.991)
Left kidney	0.889 (0.730; 0.957)	0.948 (0.866; 0.980)	0.965 (0.908; 0.987)

3 Data are presented as ICC estimates with 95% confidence intervals in parentheses.

4 LVBP, left ventricular blood pool; AA, abdominal aorta; FOV-A, field of view A; FOV-B, field of view B. AA are
5 using the mean β -value as recovery coefficient.

6

7 Under the assumptions described in Methods and using equations 2-4, total flow values were

8 estimated (Table 5). Total RPF and RBF were estimated to be 628 ± 95 ml/min/ 1.73 m^2 and $1091 \pm$

9 162 ml/min/ 1.73 m^2 , respectively.

10 **Table 5** Estimation of RPF and RBF based on ^{82}Rb clearance values (K_1) using mean β -corrected
11 AA activity in FOV-B

Average K_1 (ml/min/ cm^3)	Total renal volume (cm^3)	Total ERPF (ml/min)	Total RPF (ml/min)	Average Hct	Total RBF (ml/min)
2.04 ± 0.31	296 ± 30	603 ± 90	677 ± 102	0.42 ± 0.02	1176 ± 183

12 Data are presented as means $\pm$ SD. Total ERPF is calculated as the product of K_1 and total kidney volume. Total RPF is
13 estimated from ERPF using an assumed EF of 0.89 [19]. ERPF, effective renal plasma flow; RPF, renal plasma flow;
14 Hct, haematocrit; RBF, renal blood flow.

15

16 Discussion

17 This study confirms that RBF estimation based on ^{82}Rb PET/CT using AA as the IF in a 1-tissue

18 compartment model is feasible, as previously demonstrated by Tahari et al. (21). Additionally, our

19 results support the use of the β -corrected AA-VOI in a single FOV as an alternative IF to the

20 LVBP. The low intra-assay coefficients of variation are acceptable with good to excellent inter-

21 observer reliability, thus allowing estimated RBF to be determined using single FOV assessment of

22 the kidneys in their entirety. However as discussed below, we believe the renal clearance of ^{82}Rb

23 (K_1), to represent ERPF, rather than direct estimation of RBF.

24 ^{82}Rb as renal perfusion tracer

1 There are many advantages to using ^{82}Rb PET/CT for measurement of renal perfusion: it is non-
2 invasive and does not require blood sampling or urine collection, making the procedure less
3 burdensome for patients; it allows for single kidney blood flow estimation and is readily available
4 from $^{82}\text{Sr}/^{82}\text{Rb}$ generators which are already in-situ at sites routinely using ^{82}Rb for assessment of
5 myocardial blood flow, thus making it cost effective. In comparison, the "ideal tracer" – ^{15}O -water –
6 can be utilized only in centres with on-site cyclotron access (30). The combination of a short ^{82}Rb
7 half-life of 75 seconds and short acquisition time allows for repeated scans of the same subject
8 within a short timeframe, presenting unique opportunities to examine acute effects of differing
9 drugs on renal perfusion. For example, ^{82}Rb PET/CT may be especially suitable for use in cross-
10 over studies exploring interventional effects.

11 No absolute contraindications exist to the use of ^{82}Rb , thus patients suffering from all stages of AKI
12 and CKD can undergo the examination without risk of deterioration of renal function.

13 Since renal ^{82}Rb accumulation exceeds myocardial ^{82}Rb accumulation, half the tracer dose of
14 cardiac studies is sufficient to perform good quality renal imaging, resulting in a low effective
15 radiation dose (~ 1 mSv) for a single scan of the kidneys in their entirety, including the AA for use
16 as IF. Additionally, for modern digital scanners with high sensitivities, even lower tracer doses may
17 be sufficient to perform the examination.

1 **Input functions**

2 Pharmacokinetic modelling requires an IF, where sampling of peripheral arterial blood to produce
3 an arterial TAC is the gold standard method for obtaining an accurate estimation. However, the
4 short half-life of ^{82}Rb necessitates an alternative to the arterial sampling derived input curve. This
5 can be achieved using image derived curves based on e.g. PET/CT scanning, where LVBP and AA
6 are examples of IDIFs. Accurate IDIF estimation requires calibration of the ^{82}Rb -tracer injector
7 system and imaging scanner with associated dose calibrators to ensure accurate voxel activity
8 concentrations in the acquired images.

9 We obtained IDIFs from TACs based on VOIs placed in both LVBP and AA in the dynamic PET
10 images. Use of IDIFs based on large-size vascular structures, combined with the high resolution of
11 modern PET scanners, reduces PVE in activity measurement (31, 32). However, due to the
12 significant uptake of ^{82}Rb activity in the left ventricular wall, LVBP was corrected for PVE and
13 spill-over by applying the method of Katoh et. al, (27). It is unclear whether LVBP activity was
14 corrected for PVE and spill-over by Tahari et al. (21), however our K_1 values obtained from β -
15 corrected LVBP activity are comparable to their values. Likewise, the uncorrected activity in the
16 AA is observed to be lower than LVBP activity in both studies. Tahari et. al. (21) assessed the
17 effect to arise from PVE and as a first approximation, corrected by scaling AA activity to match the
18 observed maximum LVBP activity. It is uncertain whether the lower AA activity is solely due to
19 PVE, or whether other effects contribute to the observed peak differences. In this study we have
20 adapted the methodology described by Katoh et. al (27), where the effects to be corrected for are
21 combined in the recovery coefficient β . For isotopes with half-lives that allow for physical blood
22 sampling and well-counter measurement, the blood activity levels can be determined for calculation
23 of the β -coefficient; this is not possible for ^{82}Rb .

24 Thus, estimation of β was performed using systematic application of differing β -values to identify
25 an optimal solution for each subject in the study, with the mean β -value for all subjects determined

1 as 0.69 ± 0.09 . For comparison, a simple scaling of AA activity with respect to the peak activity or
2 area-under-curve ratios for AA and LVBP, gave estimates for correction factors which were almost
3 identical to β estimated using the method applied here. Furthermore, our K_1 results using β -
4 corrected AA activity are comparable to those obtained from AA in the study by Tahari et al.

5 Overall, good agreement is observed between the estimated activity curves for both IFs and renal
6 curves (Fig. 8) and our results for K_1 in this and Tahari's study (21).

7 For both AA and LVBP, the intra-assay coefficients of variation are acceptably low, indicating that
8 ^{82}Rb PET/CT is a precise method for evaluation of K_1 , hence allowing for determination of changes
9 in K_1 .

10 The inter-observer variability assessment supports the use of AA as IF as a robust image-derived
11 method for determining renal perfusion, with excellent reliability demonstrated for both kidneys in
12 their entirety and AA in the same FOV (FOV-B) and good to excellent reliability for AA in FOV-A,
13 compared to moderate to excellent reliability using LVBP.

1 **Renal clearance - measurement of K_1 , estimation of ERPF and RBF**

2 High renal ^{82}Rb uptake and accumulation were confirmed. To avoid errors in uptake estimation
3 caused by regional differences, it is important to measure uptake in the entire kidney. In our study,
4 13 out of 18 completing subjects (72%) showed both LVBP and the entire kidneys in FOV-A, such
5 that 5 analyses were performed on truncated kidneys. In the article by Tahari et al., only 3 out of 8
6 subjects (38%) had the LVBP and kidneys in the same FOV (corresponding to FOV-A) and 5 out of
7 8 subjects had the LVBP and kidneys in separate acquisitions. As a global quality control, we found
8 no significant difference between K_1 values derived from AA activity curves in FOV-A and those in
9 FOV-B, supporting the assumption that in the studied population with healthy, lesion-free kidneys,
10 quantitation obtained from truncated images of the kidney tissue is representative of values which
11 would be obtained from imaging the kidneys in their entirety.

12 The accuracy of ^{82}Rb PET/CT for RBF estimation cannot be evaluated in the present study.
13 Myocardial ^{82}Rb extraction is flow-dependent with a roll-off in extraction observed at increasing
14 flow rates (33, 34). If this is also the case for renal extraction, K_1 , and hence renal perfusion, may be
15 underestimated; not only with respect to the absolute values, but also relatively compared to flow-
16 values measured below the extraction roll-off point. As such, this requires further investigation, e.g.
17 by comparison with RBF measurements using the non-flow-dependent tracer, ^{15}O -water (30).

18 Using 1 cm^3 equivalence to 1 g of tissue, individual kidney volumes can be approximated from the
19 volumes encompassed by the kidney VOIs, allowing conversion of K_1 values ($\text{ml}/\text{min}/\text{cm}^3$) to total
20 flow values for both kidneys (ml/min). Total flow values are summarized in Table 5.

21 Our clearance values expressed as ERPF (Table 5) are low when compared to generally accepted
22 values for RBF: $\sim 1000\text{-}1200\text{ ml}/\text{min}$ (35); however, they are similar to previously published values
23 for ERPF with values $420\text{-}640\text{ ml}/\text{min}$ (36, 37). This strongly suggests we may actually be
24 estimating RPF and not RBF as is the current understanding.

1 Whether we measure estimated RBF or ERPF with ^{82}Rb depends on the distribution of the tracer
2 between plasma and erythrocytes in whole blood. Early studies of potassium permeability showed a
3 very slow exchange of radioactive potassium and rubidium between plasma and erythrocytes
4 amounting to 1.8-2.1% per hour and even less over 8 minutes of study (24, 25). Hence, most ^{82}Rb is
5 present in the plasma during renal uptake studies, implying the measured renal uptake values
6 represent estimated RPF after correction for extraction, if EF is close to unity. Assuming our data
7 represents RPF, estimated RBF can be calculated by correcting with the haematocrit value which is
8 easily measured; the results of which are presented in Table 5.

9 For canines, EF is estimated to be 0.89 (0.80-0.95) (19), but to our knowledge remains to be
10 determined in humans due to difficulty in calibrating and measuring blood activity for ^{82}Rb .
11 However, if we assume the extraction values to be similar for humans, we find an average total
12 estimated RBF value normalized to BSA of $1091 \pm 162 \text{ ml/min/1.73 m}^2$, which is within the
13 expected range for RBF in healthy subjects.

14 **Study strengths and limitations**

15 The major strengths of this study are a combination of the randomized cross-over design, the
16 standardization of pre-scan conditions (fluid intake, exercise level, duration of fasting period), and
17 the consecutive acquisition of the four ^{82}Rb PET/CT scans over a short 45-minute period; enabling
18 optimal evaluation of intra-assay coefficients of variation and hereby precision.

19 The homogeneous study population consisted of healthy adults, providing estimated RBF
20 measurements uninfluenced by age and medical therapy. However, this is also a potential bias as it
21 is not certain results from this study can be directly applied to a population of elderly subjects, nor
22 to subjects suffering from hypertension or renal disease; additional feasibility studies may be
23 needed for these populations. Additionally, before ^{82}Rb PET/CT can be implemented for clinical
24 estimated RBF determination, further evaluation is required of day-to-day variation as well as the

1 quantitative accuracy of the method; ideally by comparison of K_1 determined using ^{82}Rb and ^{15}O -
2 water PET/CT.

3 **Conclusion**

4 The results presented in this study, for a population of healthy subjects, support the use of an AA
5 IDIF in the 1-tissue compartment model as an alternative to LVBP; it is sufficient to determine
6 estimated RBF using a single FOV including AA and kidneys in their entirety using a single
7 dynamic ^{82}Rb PET/CT scan. Use of AA gave rise to an acceptably low intra-assay coefficient of
8 variation (~5%) and good to excellent inter-observer reliability.

9 Our data suggests that the actual flow values measured by ^{82}Rb most likely represent ERPF rather
10 than RBF which is essential for the correct interpretation of future perfusion studies using ^{82}Rb .

11 **Abbreviations**

12 AA: abdominal aorta; AKI: Acute kidney injury; ALAT: Alanine aminotransferase; BMI: Body
13 mass index; BSA: Body surface area; CI: Confidence interval; CKD: Chronic kidney disease; CT:
14 Computed tomography; EF: Extraction fraction; ERPF: Effective renal plasma flow; FOV: Field of
15 view; ICC: Intra-class correlation coefficient; IDIF: Image-derived input function; IF: Input
16 function; LVBP: Left ventricular blood pool; MBq: Megabecquerel; mCi: Millicurie; mSv:
17 MilliSievert; ^{15}O water: oxygen-15 labeled water; PET: Positron emission tomography; p.i.: Post
18 injection; PVE: Partial volume effect; ^{82}Rb : Rubidium-82; RBF: Renal blood flow; ^{82}Sr : Strontium-
19 82; SD: Standard deviation; TAC: time activity curve; VOI: volume of interest.

20 **Declarations**

21 **Ethics approval and consent to participate**

23 The study was approved by the Regional Scientific Ethics Committee (journal number: 1-10-72-
24 175-16), the Danish Medicines Agency (EudraCT-number: 2016-004080-39), the Danish Data

1 Protection Agency, and was conducted in agreement with the Declaration of Helsinki 2013.

2 Informed written consent was obtained from all participants.

3 **Consent for publication**

4 Informed consent was obtained from all participants regarding publishing of data.

5 **Availability of data and materials**

6 The datasets and trial protocol (Danish) are available from the corresponding author on reasonable
7 request.

8 **Competing interest**

9 The authors declare that they have no competing interest.

10 **Funding**

11 The study was supported by The Axel Muusfeld Foundation and The Research Foundation of the
12 Central Denmark Region.

13 14 **Authors' contributions**

15 Study concept & design: all authors; Method implementation, creation & validation of analysis
16 tools: JT, CF; Data acquisition: SSL; Data analysis: SSL, JT; Data interpretation: SSL, JT, CF;
17 drafting of manuscript: SSL; Critical revision: SSL, JT, CF, JNB; Approval of final manuscript: all
18 authors.

19 **Acknowledgements**

20 The authors thank all the Medical Laboratory Technologists involved in the practical performance
21 of this study protocol: Malene Skov Hansen & Mette Emtkjær Mølgaard (PET/CT scanning) and
22 Henriette Vorup Simonsen & Kirsten Nygaard (blood sample analysis).

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13 **Figure legends**

14 **Fig. 1** Study design

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16 **Fig. 2** Anatomical contents within the 22cm axial FOV for an example study image (subject 2): a) FOV-A: bed position
17 includes LVBP, AA and kidneys (body length and kidney size determine whether the kidneys can be seen in their
18 entirety within the FOV); b) FOV-B bed position includes AA and kidneys in their entirety

19

1 **Fig. 3** 1-tissue compartment model used for estimation of RBF. K_1 is the rate constant for ^{82}Rb uptake in the kidneys
2 from the vascular space, whereas k_2 is the rate constant for release of ^{82}Rb back into the blood. No discernible tracer
3 activity was observed via urinary excretion (21)

4
5 **Fig. 4** VOIs were drawn in a) myocardium, b) left ventricular blood pool, c) abdominal aorta (orange) and aortic
6 background (purple) and d) contouring the kidneys (green – right; cerise - left)

7
8 **Fig. 5** Participant flow in the study

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10 **Fig. 6** Typical time activity curves from the left ventricular blood pool and the myocardium from one of the study
11 subjects

12
13 **Fig. 7** a) Representative time activity curves from the various input organs and the aortic background from one of the
14 study subjects; b) Magnification of activity peaks (highlighted red box), and c) Magnification of content in the
15 highlighted blue box

16
17 **Fig. 8** Typical time activity curves from the left ventricular blood pool, abdominal aorta, and the kidneys from one of
18 the study subjects

19 **Fig. 9** Typical example of a) coronal and b) transaxial PET/CT images of kidneys during maximal ^{82}Rb uptake from
20 one of the study subjects. Shown example is for FOV-B

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Figures

Figure 1

Study design

Figure 2

Anatomical contents within the 22cm axial FOV for an example study image (subject 2): a) FOV-A: bed position includes LVBP, AA and kidneys (body length and kidney size determine whether the kidneys can be seen in their entirety within the FOV); b) FOV-B bed position includes AA and kidneys in their entirety

Figure 3

1-tissue compartment model used for estimation of RBF. K_1 is the rate constant for ^{82}Rb uptake in the kidneys from the vascular space, whereas k_2 is the rate constant for release of ^{82}Rb back into the blood. No discernible tracer activity was observed via urinary excretion (21)

Figure 4

VOIs were drawn in a) myocardium, b) left ventricular blood pool, c) abdominal aorta (orange) and aortic background (purple) and d) contouring the kidneys (green – right; cerise - left)

Figure 5

Participant flow in the study

Figure 6

Typical time activity curves from the left ventricular blood pool and the myocardium from one of the study subjects

Figure 7

a) Representative time activity curves from the various input organs and the aortic background from one of the study subjects; b) Magnification of activity peaks (highlighted red box), and c) Magnification of content in the highlighted blue box

Figure 8

Typical time activity curves from the left ventricular blood pool, abdominal aorta, and the kidneys from one of the study subjects

Figure 9

Typical example of a) coronal and b) transaxial PET/CT images of kidneys during maximal ^{82}Rb uptake from one of the study subjects. Shown example is for FOV-B