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ORIGINAL ARTICLE

Renal clearance estimated by rubidium-82 positron emission tomography/computed tomography and technetium-99m-mercaptoacetyltriglycine clearance infusion technique

Stine Sundgaard Langaa[1] | Camilla Lundgreen Duus[1] | Marie Houmaa Vrist[1] | Frank Holden Mose[1] | Claire Anne Fynbo[2] | Jørn Theil[2,3] | June Anita Ejlersen[2] | Jesper Nørgaard Bech[1,3]

[1]University Clinic in Nephrology and Hypertension, Department of Medicine, Gødstrup Hospital and Aarhus University, Herning, Denmark

[2]Clinic for Nuclear Medicine, Gødstrup Hospital, Herning, Denmark

[3]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

Correspondence

Stine Sundgaard Langaa, University Clinic in Nephrology and Hypertension, Department of Medicine, Gødstrup Hospital, Hospitalsparken 15, 7400 Herning, Denmark.
Email: stinlg@rm.dk

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Abstract

Background: Although numerous techniques exist for renal blood flow (RBF) estimation, none of the methods have been implemented in routine clinical practice due to their inadequacies and burdensomeness. Previously, we evaluated rubidium-82 (^{82}Rb) positron emission tomography/computed tomography (PET/CT) for renal perfusion determination and found strong indications of method precision and reliability. The aim of this study was to compare renal ^{82}Rb clearance with renal technetium-99m-mercaptoacetyltriglycine ([^{99m}Tc]Tc-MAG3) clearance as a first attempt to validate ^{82}Rb PET/CT for renal perfusion estimation using a reference method.

Methods: Ten subjects with essential hypertension underwent two treatment periods, receiving spironolactone and placebo in random order. At the end of each period, each subject completed a ^{82}Rb PET/CT scan and a [^{99m}Tc]Tc-MAG3 clearance study.

Results: ^{82}Rb clearance correlated positively with [^{99m}Tc]Tc-MAG3 clearance in both treatment periods. The [^{99m}Tc]Tc-MAG3-to-^{82}Rb clearance ratio was 0.83 and 0.86 in the placebo and spironolactone treatment periods, respectively.

Conclusion: The correlation between ^{82}Rb clearance and [^{99m}Tc]Tc-MAG3 clearance may indicate that PET/CT determined ^{82}Rb clearance can act as an estimator of renal perfusion. The [^{99m}Tc]Tc-MAG3-to-^{82}Rb clearance ratios suggest that the extraction fraction of ^{82}Rb is higher than that of [^{99m}Tc]Tc-MAG3, further suggesting ^{82}Rb clearance as an estimator of flow. However, further studies are warranted to validate use of ^{82}Rb PET/CT for flow estimation.

KEYWORDS

correlation, effective renal plasma flow, essential hypertension, interventional study, renal blood flow

1 | INTRODUCTION

Numerous methods are currently available for determination of renal plasma flow (RPF) or renal blood flow (RBF) in humans such as clearance-based techniques, computed tomography (CT), magnetic resonance and ultrasonography (Brodwall, 1964; Eikefjord et al., 2017; Gillis et al., 2016; Jaschke et al., 1990; Kalantarinia et al., 2009; Stadalnik et al., 1980).

Para-aminohippurate (PAH) clearance measurement using the constant infusion technique is still considered the gold standard for effective renal plasma flow (ERPF) estimation due to an almost complete renal extraction of PAH (~90%) (Battilana et al., 1991; Brodwall, 1964; Warren et al., 1944). As the PAH production is cumbersome and the chemical analysis procedure lengthy, alternative renal tubular clearance substances such as ortho-iodohippurate (OIH) labelled with either 131I or 123I and [^{99m}Tc]Tc-MAG3 have been examined for ERPF estimation.

OIH is a PAH analogue; however, the extraction fraction is lower (Maher et al., 1971; Stadalnik et al., 1980), resulting in a OIH-to-PAH clearance ratio of about 0.9 (Blaufox et al., 1967; Burbank et al., 1961; Skov & Hansen, 1974). OIH clearance has been used routinely for ERPF evaluation in research settings, however, its use in clinical settings is limited by low availability and somewhat high costs.

The [^{99m}Tc]Tc-MAG3-to-OIH clearance ratio has been reported to be about 0.5–0.6 (Jafri et al., 1988; Prenen et al., 1991; Rehling et al., 1995; Russell et al., 1988). Thus, [^{99m}Tc]Tc-MAG3 clearance underestimates ERPF by up to 50%. Nevertheless, [^{99m}Tc]Tc-MAG3 is considered a useful substitute for OIH as an approximate estimator of ERPF, primarily due to its strong and positive correlation with OIH clearance (Rehling et al., 1995; Russell et al., 1988), favourable imaging properties, low costs and by being readily available.

None of the above-mentioned techniques for RPF or RBF assessment have been implemented in routine clinical practice due to their cumbersomeness and shortcomings, hence development of a precise, reliable, straightforward and available method for renal flow estimation is warranted.

In our previous studies, we verified that estimation of renal perfusion by ^{82}Rb PET/CT is feasible (Langaa et al., 2021). Furthermore, we found indications of method precision (Langaa et al., 2021) and displayed that the day-to-day variation in ^{82}Rb clearance was low enough to allow for the detection of genuine changes in renal flow induced by amino-acid loading (Langaa et al., 2022). Based on these results, we concluded that use of ^{82}Rb PET/CT seems suitable for crossover studies aiming to evaluate changes in renal perfusion after interventions.

The aim of this paper was to compare ^{82}Rb PET/CT with [^{99m}Tc]Tc-MAG3 renal clearance measured by the constant infusion technique in a first attempt to validate ^{82}Rb PET/CT for renal perfusion estimation using a reference method.

2 | MATERIALS AND METHODS

2.1 | Data

The clearance data for this paper were obtained from a randomized, double-blinded, cross-over study examining the effect of spironolactone compared with placebo on renal hemodynamics in essentially hypertensive patients (Langaa et al., 2021, unpublished data).

2.2 | Participants

Subjects were recruited by advertisement in the local newspaper. Prior to enrolment, all participants completed a screening programme consisting of a medical history, physical examination, electrocardiography, various blood and urine analyses and ambulatory blood pressure measurements of untreated blood pressure. If untreated ambulatory blood pressure exceeded a pre-defined value of 150/95 mmHg, study subjects were prescribed metoprolol treatment as this is shown not to produce significant alterations in RPF after weeks of its use (Erley et al., 1993; Sugino et al., 1984). The prescribed metoprolol dose was unchanged during the entire study period.

No other antihypertensive treatment was allowed during the study period except for the study drug spironolactone.

2.3 | Pre-examination preparation

Each hypertensive subject completed a spironolactone treatment period and a placebo treatment period in random order. Both treatment periods were concluded by 2 examination days: a ^{82}Rb PET/CT scan examination day at the Department of Nuclear Medicine, Herning Hospital followed by a [^{99m}Tc]Tc-MAG3 clearance infusion study day at the University Clinic of Nephrology and Hypertension, Holstebro Hospital.

Four days prior to the ^{99m}Tc-MAG$_3$ clearance infusion examination day, subjects ingested a standard diet as described previously (Rosenbæk et al., 2018). Fluid intake was standardized to 35 mL/kg body weight/day and included maximum two small cups of coffee or tea per day. Intake of alcohol and soft drinks was not allowed, and no strenuous exercise was permitted in the 4 day-preparation period.

2.4 | Radiopharmaceuticals

2.4.1 | Rubidium-82

^{82}Rb is produced in a generator by the radioactive decay of strontium-82 (Cardiogen-82; Bracco Diagnostics Inc.). The generator was quality checked on each examination day in accordance with approved guidelines (Bracco Diagnostics Inc.), including tests for

possible strontium breakthrough. Calibration allowed the generator to deliver an activity of 555 megabecquerel (MBq) ^{82}Rb for each bolus injection.

2.4.2 | [^{99m}Tc]Tc-MAG3

Commercial kits (TechneScan MAG_3, Curium Netherlands B.V.) were used to prepare [^{99m}Tc]Tc-MAG3 solutions in accordance with manufacturer instructions. Thin-layer chromatography was used to test new batches for radiochemical purity (> 95%).

2.4.3 | PET/CT scans

All PET/CT scans were performed using a designated PET/CT scanner (Siemens Biograph mCT; 64 slice-4R) with an axial field of view of 22 cm at the Department of Nuclear Medicine, Herning Hospital, Denmark. The PET/CT scanner was quality checked and calibrated in accordance with approved guidelines at the beginning of each examination day.

On ^{82}Rb PET/CT scan examination days, subjects arrived at ~8.30 AM after an overnight fast. Pregnancy was ruled out in fertile women. Pre-scan preparation of subjects, acquisition of PET/CT scans and re-binning and reconstruction of list-mode data were conducted as previously described (Langaa et al., 2022).

2.4.4 | [^{99m}Tc]Tc-MAG3 clearance

[^{99m}Tc]Tc-MAG3 clearance was determined by the constant infusion technique (Østergaard et al., 2021; Prenen et al., 1991).

Subjects arrived at 7.45 AM after an overnight fast at the University Clinic of Nephrology and Hypertension, Holstebro Hospital, Denmark. Pregnancy was ruled out in fertile women. The subjects were placed in a quiet and temperature-controlled room (22°C–25°C) in a supine position. A catheter was placed in a cubital vein in each arm for blood sampling and for infusion of [^{99m}Tc]Tc-MAG3. To ensure sufficient urine flow, oral loading with 175 mL tap water was commenced at 8.00 AM and repeated every 30 min until the end of the examination day.

At 9.00 AM a 32 mL priming dose of [^{99m}Tc]Tc-MAG3 with a concentration of 1.25 MBq/mL was administered, immediately followed by a sustained [^{99m}Tc]Tc-MAG3 infusion with the same concentration using a volume-controlled infusion pump (Alaris TIVA, Cardinal Health) programmed to a rate of 8 mL/h to keep plasma activity stable throughout the day. The infusion was terminated at 1.30 PM. Blood samples drawn at 10 AM and every half hour until 1.30 PM were centrifuged immediately upon collection. Urine samples were collected by voiding standing or sitting at 10.30 AM, 11.30 AM, 12.30 PM and 1.30 PM. Immediately after the infusion was terminated, ^{99m}Tc-MAG_3 activity in plasma and urine was counted in duplicate in an automatic gamma counter (Wizard2, PerkinElmer).

2.5 | Dosimetry

A low-dose CT scan contributed with 0.4 milliSievert (mSv), each ^{82}Rb bolus injection contributed with 0.7 mSv (1.26 μSv/MBq), and a [^{99m}Tc]Tc-MAG3 clearance study contributed with 0.7 mSv resulting in a total effective radiation dose of 3.6 mSv.

2.6 | Analysis of ^{82}Rb PET/CT studies

Using a 1-tissue compartment model, the K_1-parameter represents renal ^{82}Rb clearance (mL/min/cm^3) from blood to tissue and can, as a result of high (~ 90%) first pass extraction of ^{82}Rb in the kidneys (Mullani et al., 1990), be considered an estimator of flow (Langaa et al., 2021, 2022; Tahari et al., 2014).

Pharmacokinetic modelling was done in PMOD (PMOD Technologies Ltd., Zurich, Switzerland, version 4.102) resulting in K_1 values being determined for each kidney as described previously (Langaa et al., 2022) with the following modifications: plasma corrected input curves were used and the fractional blood volume within kidney VOIs was fitted.

Total renal ^{82}Rb clearance was estimated based on the K_1 values and computer-estimated kidney volumes (cm^3) and normalized to body surface area (BSA) (Langaa et al., 2022).

2.7 | Analysis of [^{99m}Tc]Tc-MAG3 clearance studies

On both examination days, steady-state [^{99m}Tc]Tc-MAG3 plasma concentration was reached ~150 min after infusion start and was maintained for the remainder of the infusion. This enabled the determination of two steady-state renal plasma clearances which were averaged to give one clearance value.

Renal plasma clearance was calculated using the formula:

$$\text{Renal plasma clearance} = \frac{Ux^{*}V}{P} \quad (1)$$

where Ux is urine activity (counts per minute (cpm)/mL), V urine volume per minute (mL/min) and P plasma activity (cpm/mL). Due to the difference in sampling rates for urine (every hour) and plasma (every half-hour), in order to match the measured plasma activity to the urine sampling timeframe, the plasma activity values used for the calculation were the mean of the plasma activity at the urine sample time and the plasma activity 30 min earlier.

Using the Du Bois formula (Du Bois and Du Bois, 1989), clearance values were normalized to BSA:

$$BSA = 0.007184 \cdot height^{0.725} \cdot weight^{0.425}. \quad (2)$$

Units: BSA (m^2), height (cm) and weight (kg).

2.8 | Statistical analysis

Statistical tests were performed using SPSS Statistics ver. 20 (IBM Corp.). Test of data normality was performed using Q–Q plots. Normally distributed data are presented as means with SD or range. Statistical significance was defined as $p < 0.05$. Correlation analyses were performed using Pearson's correlation for normally distributed data. Bland–Altman plots were used to assess agreement between methods (Altman & Bland, 1983).

2.9 | Ethics

The study was approved by the Regional Scientific Ethics Committee (Journal Number: 1-10-72-100-19), the Danish Medicines Agency (EudraCT-number: 2019–001636–60), the Danish Data Protection Agency, and was conducted in agreement with the Declaration of Helsinki 2013. Written informed consent was attained from all participants prior to any study-related activities.

3 | RESULTS

3.1 | Demographics

Of 32 hypertensive patients assessed for eligibility in the study, 16 subjects were randomized with 10 subjects completing the study (Figure 1). Characteristics of completing subjects are given in Table 1.

3.2 | Renal clearances

Table 2 presents ^{82}Rb and [^{99m}Tc]Tc-MAG3 renal clearances normalized to BSA for the 10 completing subjects (A–J) in both treatment periods.

Treatment with spironolactone did not significantly alter renal clearance compared to placebo treatment, regardless of whether clearance was determined using ^{82}Rb-PET/CT ($p = 0.117$) or [^{99m}Tc]Tc-MAG3 techniques ($p = 0.233$). However, as displayed in Figure 2, the flow changes in response to spironolactone treatment were widely variable for both tracers.

The correlation between renal ^{82}Rb clearance and [^{99m}Tc]Tc-MAG3 clearance is displayed in Figure 3. The Pearson correlation coefficients (r) being 0.72 ($p = 0.019$) and 0.63 ($p = 0.053$) in the placebo and spironolactone periods, respectively.

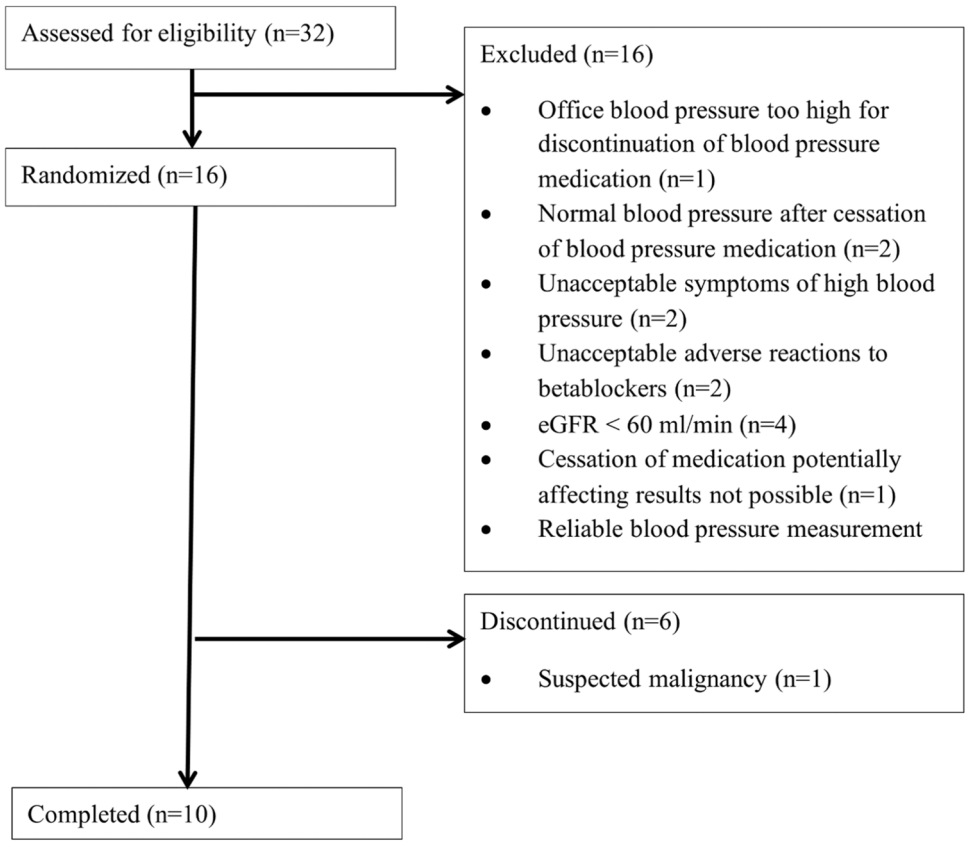

FIGURE 1 Participant flow chart.

TABLE 1 Clinical and biochemical characteristics ($n = 10$).

Age (years)	66 (53–76)
Gender (women/men)	3/7
Body mass index (kg/m^2)	25.0 ± 8.6
Ambulatory systolic blood pressure (mmHg)[a]	156 ± 11
Ambulatory diastolic blood pressure (mmHg)[a]	87 ± 10
Heart rate (beats/min)	66 ± 10
P-creatinine (μmol/L)	81 ± 12
$eGFR_{CKD\text{-}EPI}$ (mL/min/1.73m^2)	81 ± 14

Note: Data are presented as mean ± SD or as mean with range.
Abbreviation: eGFRCKD-EPI, estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.
[a]Untreated blood pressure.

The overall [^{99m}Tc]Tc-MAG3-to-^{82}Rb clearance ratios were 0.83 ± 0.16 and 0.86 ± 0.20 for the placebo and spironolactone periods, respectively (Table 2).

Bland–Altman plots evaluating agreement between ^{82}Rb PET/CT and [^{99m}Tc]Tc-MAG3 clearance techniques for determination of renal clearance in both treatment periods are displayed in Figure 4. In both BA plots, no obvious systematic bias was observed.

Figure 5 depicts differential analysis of the flow changes between the placebo and spironolactone treatment periods using ^{82}Rb PET/CT (Figure 5a) and the [^{99m}Tc]Tc-MAG3 clearance techniques (Figure 5b). These show no obvious flow-dependent trend for changes in ^{82}Rb clearance measurements, whereas a positive trend is observed for changes in [^{99m}Tc]Tc-MAG3 clearance measurements, indicating that this method appears to be clearance-dependent.

4 | DISCUSSION

In this study, we have made a first attempt to validate ^{82}Rb PET/CT for renal perfusion estimation in humans using the reference method available in our laboratory: [^{99m}Tc]Tc-MAG3 clearance constant infusion technique.

4.1 | Evaluation of the renal clearances of ^{82}Rb and [^{99m}Tc]Tc-MAG3

In both treatment cycles, renal ^{82}Rb clearance correlated positively with renal [^{99m}Tc]Tc-MAG3 clearance which is an accepted approximate estimator of ERPF. The correlation in the placebo period reached statistical significance ($p = 0.019$) whereas the correlation in the spironolactone period just misses statistical significance ($p = 0.053$). The fact that the p value in the placebo period is not especially low for a correlation coefficient and that the p value in the spironolactone period is just above the significance level of 0.05 could at least partly be explained by the quite high variability in the data possibly contributing to masking of statistical significance. This variability may be caused by the relatively low number of patients and the indication that [^{99m}Tc]Tc-MAG3 is not a perfect tracer as it shows some dependence on clearance as suggested in Figure 5b.

Although the correlation between renal ^{82}Rb clearance estimated by PET/CT and renal [^{99m}Tc]Tc-MAG3 clearance is not perfect, the correlation between the renal clearances found in our study is considered indicative of ^{82}Rb clearance being used as an estimator of renal flow. However, based on our study, it cannot be determined whether one method is better than the other for flow estimation.

Regardless of whether the ^{82}Rb PET/CT or [^{99m}Tc]Tc-MAG3 technique was used for renal clearance determination, the general conclusion on the potential effect of spironolactone on renal perfusion was the same: on average, spironolactone did not alter renal clearance significantly compared with placebo. This conclusion is however not surprising due to the widely varying individual responses to spironolactone using both tracers (Figure 2). Our observed variable response to spironolactone treatment is however not unheard of. The varying responses to spironolactone agree with previous findings by (Falch et al., 1979). In a study group of the same size as ours and also consisting of subjects suffering from essential hypertension, Falch et al. (1979) found that spironolactone treatment resulted in widely variable changes in ERPF and as in our study, the average study group result showed no significant effect of spironolactone on ERPF.

The widely varying responses to spironolactone treatment using both tracers could explain why the relative changes in ^{82}Rb and [^{99m}Tc]Tc-MAG3 clearances between the placebo and spironolactone period did not correlate ($r = 0.17$).

Agreement between the two measurement methods was quantitatively assessed using Bland–Altman analysis (Altman & Bland, 1983), with the agreement between ^{82}Rb PET/CT and [^{99m}Tc]Tc-MAG3 clearance techniques shown in Figure 4. For both treatment periods, no obvious systematic bias was observed. Further differential analysis of the flow changes between the placebo and spironolactone series for each tracer (Figure 5), indicates that [^{99m}Tc]Tc-MAG3 may be flow-dependent, whereas ^{82}Rb appears to be flow-independent.

The [^{99m}Tc]Tc-MAG3-to-^{82}Rb clearance ratio in the placebo period was 0.83 ± 0.16 and in the spironolactone period 0.86 ± 0.20, suggesting that the extraction fraction of ^{82}Rb is higher than that of [^{99m}Tc]Tc-MAG3. Thus, our findings may indicate that ^{82}Rb clearance determined by PET/CT can act as an estimator of renal flow.

4.2 | Comparison of [^{99m}Tc]Tc-MAG3 clearance values with the existing literature

The mean [^{99m}Tc]Tc-MAG3 clearance of 216 ± 52 mL/min/1.73 m^2 in the placebo treatment period is considerably lower than the mean [^{99m}Tc]Tc-MAG3 clearances reported in the studies by Prenen et al. (1991) (257 ± 24 mL/min/1.73 m^2) and Taylor et al. (1988) (288 ± 53 mL/min/

TABLE 2 Renal clearances of ^{82}Rb and [^{99m}Tc]Tc-MAG3 standardized to BSA.

Subject no.	Clearance (placebo) (mL/min/1.73 m^2)		Clearance ratio Placebo [^{99m}Tc]Tc-MAG3-to-^{82}Rb	Clearance (spironolactone) (mL/min/1.73 m^2)		Clearance ratio spironolactone [^{99m}Tc]Tc-MAG3-to-^{82}Rb
	^{82}Rb	[^{99m}Tc]Tc-MAG3		^{82}Rb	[^{99m}Tc]Tc-MAG3	
A (F)	202	126	0.62	209	148	0.71
B (M)	192	189	0.98	175	171	0.97
C (M)	176	190	1.08	143	191	1.33
D (F)	210	175	0.83	238	187	0.78
E (M)	341	262	0.77	315	247	0.79
F (M)	297	263	0.89	269	247	0.92
G (M)	314	179	0.57	302	187	0.62
H (F)	317	292	0.92	342	235	0.69
I (M)	323	237	0.73	257	241	0.94
J (M)	283	244	0.86	245	204	0.83
Mean	266	216	0.83	250	206	0.86
SD	63	52	0.16	62	35	0.20
CV	0.24	0.24	0.19	0.25	0.17	0.24

Abbreviations: ^{82}Rb, rubidium-82; [^{99m}Tc]Tc-MAG3, Technetium-99m-mercaptoacetyltriglycine; BSA, body surface area, CV, coefficient of variation; F, female; M, male; SD, standard deviation.

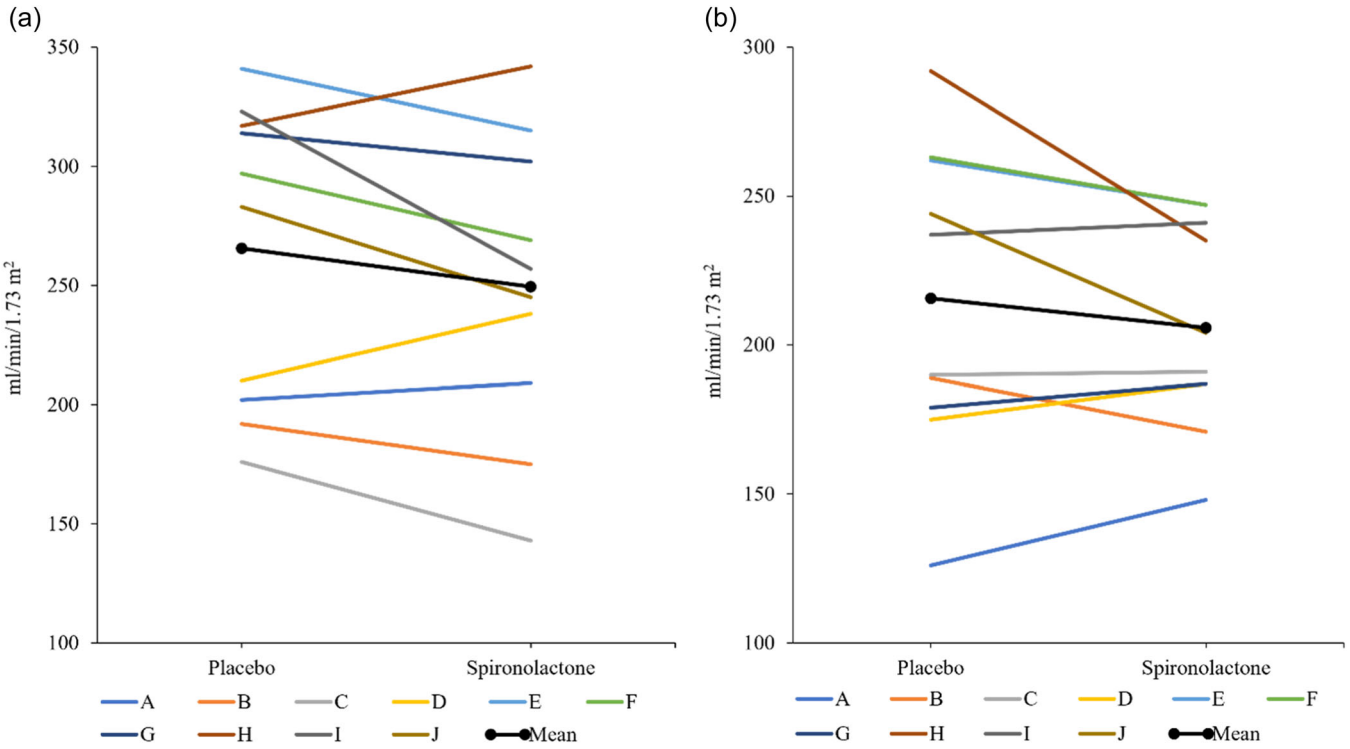

FIGURE 2 Individual ^{82}Rb clearance values (a) and [^{99m}Tc]Tc-MAG3 clearance values (b) during placebo and spironolactone treatment. [^{99m}Tc]Tc-MAG3 clearance values for subjects E and F are almost identical and thus difficult to distinguish from each other in the figure. The black bar illustrates the mean.

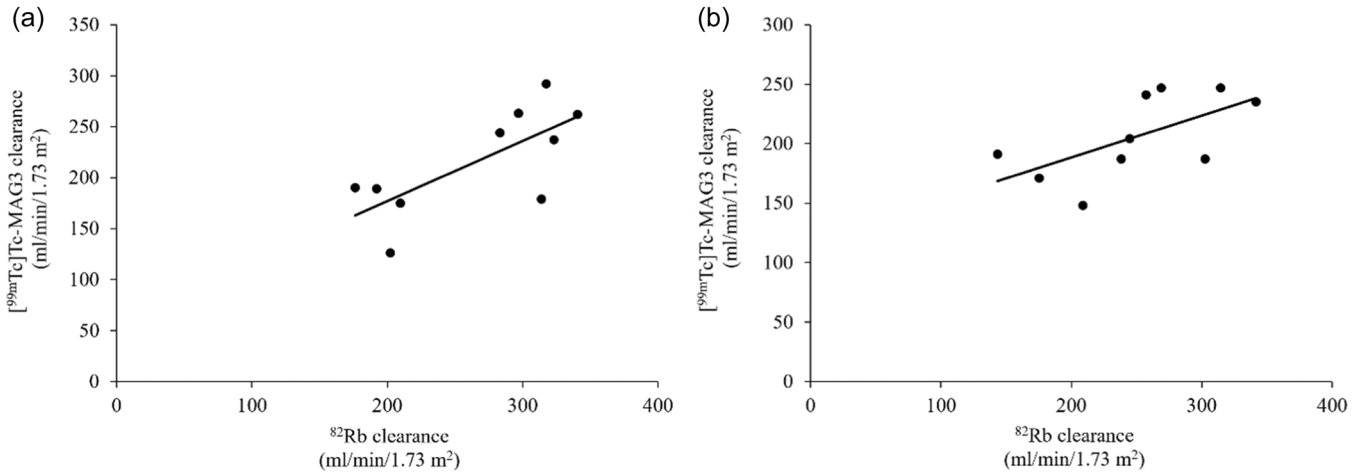

FIGURE 3 The correlation between ^{82}Rb clearance and [^{99m}Tc]Tc-MAG3 clearance in the placebo period (a) and in the spironolactone period (b). Statistical analysis is performed using Pearson's correlation.

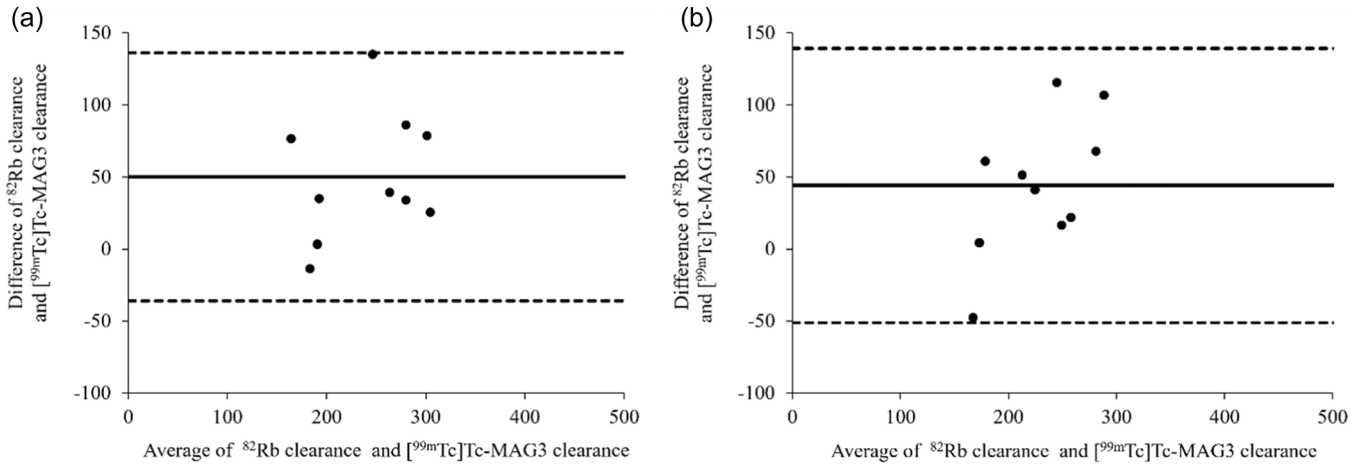

FIGURE 4 Bland-Altman plots assessing agreement between the two methods in the placebo period (a) and in the spironolactone period (b). Average of differences (solid line) and upper and lower limits of agreement (dashed lines) are shown.

1.73 m^2). However, the study subjects in Prenen's and Taylor's studies were young and healthy. Thus, the lower renal [^{99m}Tc]Tc-MAG3 clearance values in our middle-aged study subjects were fully anticipated, since ERPF decreases with age (Fliser & Ritz, 1996).

4.3 | Method accuracy

Ideally, renal clearance determined by ^{82}Rb PET/CT should be directly compared to renal clearance determined using the gold standard for ERPF estimation, PAH clearance technique. Unfortunately, neither PAH nor the PAH analogue OIH was available to us. As a consequence, in this study, the routinely used [^{99m}Tc]Tc-MAG3 constant infusion technique was chosen as the reference method as it is readily available in our laboratory and also widely accepted for ERPF approximation. However, its use in the process of validating ^{82}Rb PET/CT for renal perfusion estimation is not optimal, since ERPF is significantly underestimated when using [^{99m}Tc]Tc-MAG3 as the flow tracer agent (Jafri et al., 1988; Prenen et al., 1991; Rehling et al., 1995; Russell et al., 1988) as opposed to using PAH or OIH. Ergo, our findings can only be considered indicative of use of ^{82}Rb PET/CT for flow estimation not obtaining direct evidence and further validation attempts must be made.

Further validation studies including assessment of accuracy should ideally be based on the PAH clearance technique. Although the accuracy question still remains unanswered, use of ^{82}Rb PET/CT remains highly suitable in crossover studies aiming to evaluate changes in renal clearance after interventions.

4.4 | Study strengths and limitations

A major study strength is the standardized conditions regarding diet, fluid intake, exercise level and duration of fasting prior to the 2 examination days concluding each treatment period.

Due to a fairly strict screening process excluding patients with a variety of co-existing diseases and hypertensive complications, the

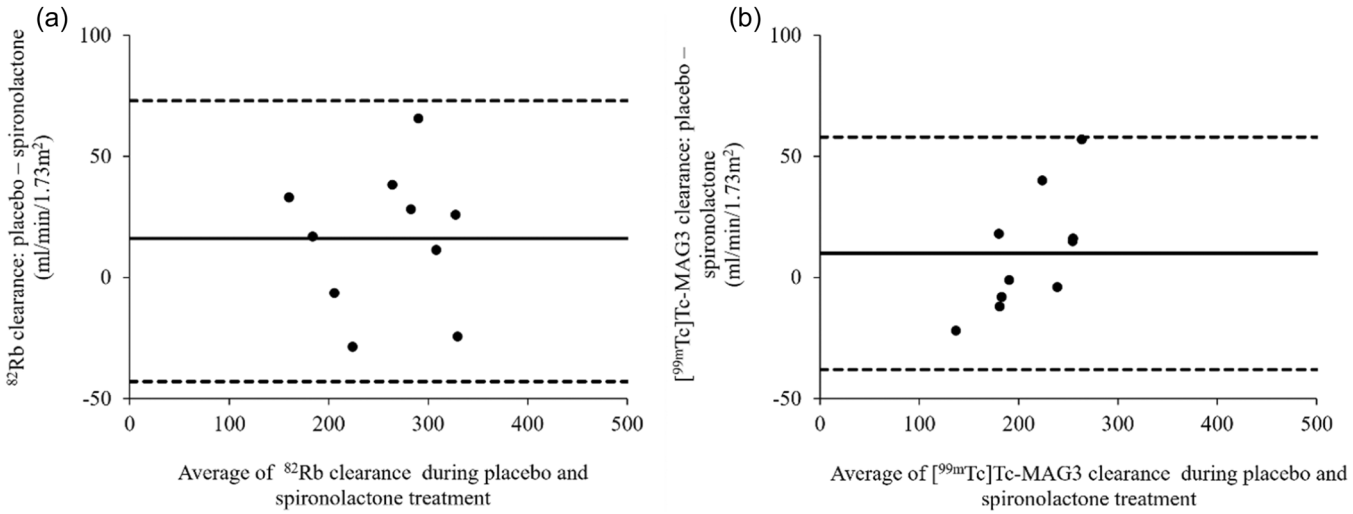

FIGURE 5 Plots assessing agreement between clearance measurements during placebo treatment and spironolactone treatment using (a) ^{82}Rb PET/CT and (b) [^{99m}Tc]Tc-MAG3 clearance technique. Average of differences (solid line) and upper and lower limits of agreement (dashed lines) are shown.

final study population consisted of relatively healthy adults with uncomplicated essential hypertension reducing potential factors influencing the results. On the other hand, the relatively homogenous study group could be seen as a potential bias as it results in our findings being less generalizable.

Renal [^{99m}Tc]Tc-MAG3 clearance calculations are directly affected by potential inaccuracies in urine collection. In this study, urine samples were collected by voiding every 60 min. Subjects with a history of voiding difficulties were not included in the study. However, without bladder catheterization the risk of incomplete bladder emptying still remains, potentially affecting [^{99m}Tc]Tc-MAG3 clearance results.

^{82}Rb PET/CT scans and [^{99m}Tc]Tc-MAG3 clearance studies could not be carried out on the same day or at the same time. However, due to the standardized conditions preceding the 2 examination days, this is not considered to have influenced the results significantly. Day-to-day variation in blood flow may influence the comparison of the two methods.

^{82}Rb PET/CT scans were of short duration (about 10 min) and carried out in the morning whereas [^{99m}Tc]Tc-MAG3 clearance studies were constant infusion studies and thus of longer duration (4.5 h) ending just after noon. Although ERPF has a circadian rhythm, the differences between renal ^{82}Rb clearance and renal [^{99m}Tc]Tc-MAG3 clearance cannot be explained by this cyclic variation, since significant changes in ERPF have been shown in the late afternoon and at night (Eckerbom et al., 2020; Koopman et al., 1989).

5 | CONCLUSION

To our knowledge, this study is the very first attempt to validate ^{82}Rb PET/CT for renal perfusion estimation in humans using a reference method. The correlation between renal ^{82}Rb clearance and clearance values determined by the [^{99m}Tc]Tc-MAG3 clearance technique may indicate that PET/CT determined ^{82}Rb clearance can act as an indicator of renal flow. The [^{99m}Tc]Tc-MAG3-to-^{82}Rb clearance ratios indicate that the extraction fraction of ^{82}Rb is higher than that of [^{99m}Tc]Tc-MAG3, further suggesting ^{82}Rb clearance as an estimator of flow. Nevertheless, further studies are warranted to validate use of ^{82}Rb PET/CT for flow estimation.

AUTHOR CONTRIBUTIONS

Study concept and design: all authors. *Data acquisition*: S. S. L., C. L. D., and M. H. V. *Data analysis*: S. S. L. *Data interpretation*: S. S. L., J. A. E., J. T. and C. F. *Drafting of manuscript*: S. S. L. *Critical revision of manuscript and approval of final manuscript*: all authors.

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CONFLICT OF INTEREST STATEMENT

Frank Holden Mose has received personal fees from Astra Zeneca. All other authors have no competing interests.

DATA AVAILABILITY STATEMENT

The data sets and trial protocol (Danish) are available from the corresponding author on reasonable request.

ORCID

Stine Sundgaard Langaa http://orcid.org/0000-0003-4525-7283

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