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PET [^{11}C]acetate is also a perfusion tracer for kidney evaluation purposes

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ABSTRACT

Rationale: Renal positron emission tomography (PET) functional imaging allows non-invasive and dynamic measurements of functional and metabolic parameters. [^{15}O]H_2O is used as a perfusion tracer, and [^{11}C]acetate as an oxidative metabolism in this purpose, requiring two injections to assess those fundamental parameters. Yet, in cardiac physiology study, the high first-pass myocardial extraction fraction of [^{11}C]acetate allowed to use its influx rate as a blood flow marker too. Since [^{11}C]acetate has been characterized by a 20–25% single pass renal extraction in dogs, it could be used as a potential tracer for renal perfusion. The aim of this study was to determine whether [^{11}C]acetate influx rate can be used as quantitative *in vivo* marker of kidney perfusion in human.
Methods: In 10 healthy subjects, dynamic PET acquisitions were performed after [^{15}O]H_2O and [^{11}C]acetate injections spaced by a 15-minute interval. As previously validated, with compartmental modeling of kinetics, renal perfusion and oxidative metabolism were estimated respectively with influx rate of [^{15}O]H_2O and efflux rate of [^{11}C]acetate. Additionally, influx rate of [^{11}C]acetate was regressed to influx rate of [^{15}O]H_2O.
Results: Renal time activity curves of [^{11}C]-acetate was best fitted with a mono compartmental model compared to a bi-compartmental model ($p < 0.0001$). [^{11}C]acetate influx rate was significantly correlated with perfusion quantified with [^{15}O]H_2O ($r^2 = 0.37$, $p < 0.001$) at baseline. This regression allowed the computation of a renal [^{11}C]acetate extraction fraction (EF), and further the computation of renal blood flow from its influx rate.
Conclusion: In healthy subjects, over a wide range of renal perfusion, direct estimates of renal oxygen consumption as well as tissue perfusion can be obtained by PET with a single tracer [^{11}C]acetate. This approach needs to be validated in CKD patients, and would be of great interest to design clinical protocol aiming at evaluating ischemic nephropathies candidate to revascularization.

1. Introduction

Renal functional parameters evaluation is important to our understanding of kidney physiology, because renal perfusion and metabolism impairments lead to chronic kidney disease progression associated with mortality [1]. Simultaneous assessment of renal perfusion and renal oxidative metabolism allows a fine evaluation of kidney response in various physiological and pathological settings because those two parameters are not linearly correlated as previously described downstream a renal artery stenosis [2]. With PET imaging, [^{15}O]H_2O is used for kidney perfusion evaluation [3], and [^{11}C]acetate allows to determine renal oxygen consumption through renal oxidative metabolism [4]. Hence, the evaluation of those two fundamental parameters requires two scan sessions leading to a significant radiation dose. Additionally, while the very short half-life of ^{15}O (2 min) can be a benefit for serial testing, it can be hard to handle in a clinical context. However, the high first-pass myocardial extraction fraction of [^{11}C]acetate allows to use its initial uptake as a blood flow marker for cardiac purposes [5] on top of oxygen consumption evaluation. Indeed, in both animal and human subjects, [^{11}C]acetate rapidly accumulates in myocardium and subsequently clears mainly in the form of CO_2 [6]. Tracer kinetic modeling of the dynamic imaging data is used to derive kinetic parameters that provide quantification of both myocardial oxidative metabolism and regional myocardial blood flow after one single injection [5]. Similarly to the heart, the kidney is an organ characterized by high levels of metabolism, particularly oxidative metabolism in the renal cortex, which allows to hypothesize that, in the kidney too, [^{11}C]acetate could

Abbreviations: AIC, Akaike information criteria; AGE, advanced glycation end products; CKD, chronic kidney disease; GFR, glomerular filtration rate; PET, positron emission tomography; RBF, renal blood flow.

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be used as a perfusion tracer. Thus, renal oxidative metabolism can be derived from [^{11}C]acetate dynamic data using arterial input function and one-tissue compartmental model [6] as demonstrated by Juillard et al. in a pig study [4].

The [^{11}C]acetate is rapidly extracted by renal cells after IV injection and its extraction is flow limited [6]. Thus, it is a good candidate to be used as a perfusion tracer, which would be of great interest to assess both renal perfusion and oxidative metabolism with a single tracer injection. Perfusion can be computed from the kinetic influx rate K1 parameter using the relationship rRBF = K1 × 1 / single-pass renal extraction fraction (EF), as far as the tracer EF is known. For [^{11}C]acetate, the single-pass renal extraction fraction has been estimated in dogs to be roughly 20 to 25% for baseline renal blood flow [6]. The aim of this study was to validate the use of [^{11}C]acetate as a renal perfusion tracer in human, using [^{15}O]H_2O as a gold standard.

2. Methods

2.1. Study design

This work is an ancillary study of a previously published study [7]. Inclusion criteria were male sex, age between 18 and 30 years, no diabetes, no hypertension, no chronic kidney disease defined as a GFR > 90 mL/min/1.73m^2 estimated by the CKD-EPI formula and/or a proteinuria/creatininuria index of >0.15 if urinary dipstick analysis showed proteinuria. The study was accepted by the local ethics committee (Comité de Protection des Personnes Sud-Est II-N°2015-52-2), on December 30th 2015, and the French National Drugs Agency (ANSM-N°1515451-11) on January 24th, 2016. It was carried out according to the principles outlined in the Declaration of Helsinki. An informed signed consent was obtained for all participants after information was given.

2.2. Procedure

Each subject underwent PET imaging sessions on two different days, separated by a minimum 1-week interval, in a crossover design, following an overnight fast. During each session, subjects were given two different high protein loads to increase perfusion and metabolism, which were evaluated with PET performed at baseline before meal, and 120 min after each meal. Perfusion was evaluated with [^{15}O]H_2O and oxygen consumption with [^{11}C]acetate. Therefore each subject benefited from both [^{15}O]H_2O and [^{11}C]acetate injections at baseline. For this study, we decided to only compare baseline perfusion values (and not post-protein loads perfusion) to increase reproducibility. PET acquisitions were performed with a PET-MRI scanner (Biograph mMR, Siemens, Germany), which allow simultaneous MRI acquisitions.

2.3. Functional imaging

2.3.1. PET with [^{15}O]H_2O

For each PET measurement, 270 MBq of [^{15}O]H_2O was injected intravenously at a constant rate over 5 s, manually. PET acquisition started simultaneously in list mode for 3 min. A dynamic series of images was reconstructed using an OP-OSEM-PSF (Ordinary Poisson-Ordered-subset expectation maximization-point-spread function) method. Series consisted in eight 4-second images, four 6-second images, six 10-second images, and four 20-second images.

2.3.2. ^{11}C-acetate-PET

For each PET measurement, 290 MBq of [^{11}C]acetate was injected intravenously at a constant rate over 5 s, using an injector. From a 20 minute dynamic acquisition, a series of ten 10-second images, ten 20-second images, two 150-second images, and two 300-second images were reconstructed using an OP-OSEM-PSF method.

2.3.3. TAC extraction and partial volume correction

For each acquisition, a static image was generated by summation of all dynamic frames on which three regions of interest (ROI) were manually drawn for time activity curve (TAC) extraction with IRW software 4.2 (Inveon Research Workplace, Siemens Healthineers Global, USA).

The aorta ROI was created around the aorta with the interpolation between two circles, one placed on the renal arteries bifurcation, and the second ten slices above the bifurcation (1 cm), on the static image, with control on the anatomical T1W image acquired at the same time of the PET acquisition. Right and left cortices ROI of the kidneys were drawn on anatomical T1W images. Time activity curves (TACs) were extracted for the aorta and each renal cortex. ROIs were used for [^{15}O]H_2O and [^{11}C]acetate data extraction.

2.3.4. Kinetic modeling

Kinetic modeling of cortical TACs was performed with aorta TAC taken as input function. No weighting was applied for modeling.

With [^{15}O]H_2O cortical renal TACs, renal blood flow (rBF) was estimated by using a one-tissue compartmental (1TC) model [3], with the K1 influx rate (K1-H_2O), including delay between aortic vascular fraction (volume of blood / volume of kidney cortex). With [^{11}C]-acetate cortical TACS, influx rate (K1-acetate) and efflux rate (k2-acetate) were compute with a one-tissue compartmental model. A two-tissue compartmental (2TC) model was fitted to [^{11}C]-acetate. AIC (Akaike information criteria) was used to evaluate fitting quality. AIC is an estimator of the relative quality of statistical model for a given set of data [8]. The lower AIC represents a better fit. Modeling was performed with pmod software (PMOD Technologies Ltd., Zurich).

2.3.5. Evaluation of perfusion measurement with [^{11}C]-acetate

For [^{11}C]-acetate, quality of fit with 1TC and 2TC were statistically assessed. Selecting the 1TC parameters, correlation between K1-H_2O and K1-acetate were evaluated using linear regression analysis for the whole data. Bland-Altman plots were generated to evaluate methodological accuracy and to assess the limits of agreement. Extraction fraction for [^{11}C]-acetate was computed from the regression. Renal blood flow (RBF) was then evaluated with K1-acetate, and reproducibility parameters (bias, typical error and intra-class correlation) of the measurement were computed with reference to RBF estimated with [^{15}O]H_2O. Reproducibility of RBF measured with [^{15}O]H_2O only was also estimated between PET sessions at baseline for comparison. A p value of <0.05 was considered statistically significant. Statistical analysis was performed using Graph Pad software (Berkeley, CA, USA).

3. Results

3.1. Patients characteristics

We included 10 healthy subjects from February to July 2016. Mean age was 22.1 ± 3.7 years, mean body weight was 65.2 ± 6.8 kg with a mean BMI of 20.8 ± 1.4 kg/m^2, and normal renal function (mean serum creatinine was 76 ± 12.3 μmol/L corresponding to a mean eGFR of 120.9 ± 12.9 mL/min/1.73 m^2). Mean blood pressure was 127/77 mmHg (Table 1).

Table 1
Subjects characteristics.

Parameters	n = 10
Age (years)	22.1 ± 3.7
Blood pressure (mmHg)	127/77 ± 12/5
Creatinine (μmol/L)	76 ± 12.3
eGFR (mL/min/1.73 m^2)-CKD-EPI	120.9 ± 12.9
Protein intake (g/kg/day)	0.6 ± 0.2
Salt intake (g/day)	4.5 ± 1.6

3.2. Confirmation of a mono compartmental model

Acetate data were best fitted using a 1TC model compared to a 2TC model with a mean AIC of 37.39 for 1TC compared to 42.80 for 2TC (paired *t*-test, $p < 0.0001$) (Fig. 1). For 61/64 cortex measurements, AIC indicated that 1T was better than 2T while for only 3/64 cortices AIC indicated that 2T was better than 1T.

3.3. Renal extraction fraction of [^{11}C]-acetate

K1 for [^{11}C]acetate and [^{15}O]water is shown in Fig. 2. Using only baseline data values, the relationship between K1-H_2O and K1-acetate was K1-acetate = 1.90 × K1-H_2O with a $r^2 = 0.37$ (Fig. 3).

Perfusion can be derived from the relationship RBF = K1 × 1 / (single-pass renal extraction fraction). While single pass extraction fraction of [^{15}O]H_2O is 1, we determined the single pass extraction fraction of acetate as being 1/1.90 = 0.52.

Using post interventional data (after protein loads), K1 [^{11}C]acetate was 1.65 × K1 [^{15}O]water corresponding to a 60% extraction fraction after the low protein load. After the high protein load responsible for a + 20% increase in RBF in mean, K1 [^{11}C]acetate was 1.95 × K1 [^{15}O] water corresponding to a lower extraction fraction of 51%.

3.4. Correlation between [^{15}O]H_2O and [^{11}C]acetate baseline perfusion

Perfusion values from acetate were then obtained using the 52% extraction fraction of [^{11}C] acetate. Baseline perfusion ranged from 2.21 to 4.48 with a mean of 3.32 ± 0.50 mL/g/min using [^{11}C] acetate data whereas it ranges from 2.00 to 4.70 with a mean of 3.29 ± 0.65 using [^{15}O] H_2O.

There was a significant correlation between renal baseline perfusion obtained from [^{11}C]acetate data and baseline perfusion from [^{15}O]H_2O data ($r^2 = 0.37$, $p < 0.001$). The Bland and Altman difference plot demonstrated a significant agreement between the two methods with a mean bias of 0.23 ± 0.6, CI 95% [1.42–0.95] (Fig. 4).

3.5. Reproducibility

For a mean bias of 0.23, the typical error of the perfusion computed from the [^{11}C]acetate compared to [^{15}O]H_2O was 0.37, with an ICC of 0.43. As a comparison, test-retest reproducibility of perfusion assessed with [^{15}0]H_2O at baseline between the two sessions had a mean bias of 0.23 with a typical error of 0.36 with an ICC of 0.64. Between sessions, test-retest reproducibility of perfusion measured with [^{11}C] acetate has a typical error of 0.22 with an ICC of 0.26 (Table 2).

4. Discussion

This study allowed to confirm that early renal uptake of [^{11}C]acetate can be used to provide an indirect quantitative evaluation of renal perfusion.

We confirmed that, as previously demonstrated [4], a one-compartment model is suitable for modeling the [^{11}C]acetate renal PET TAC, hence modeling perfusion and oxygen consumption. Indeed, the slower phase of a bi compartmental model in the heart is explained by the delayed synthesis of glutamine and acetate from a glutamate pool in the heart that does not exist in the kidney as demonstrated by Ng et al. [9]. In the kidney, there is no glutamate pool explaining the absence of need of a more complex design.

Same ROIs were used for [^{15}O]H_2O and [^{11}C]acetate data analysis, therefore the value range of K1 parameter obtained from both tracers cannot be secondary to ROIs positioning. Hence, the influx difference is explained by acetate single pass extraction. The [^{15}O]H_2O is a freely diffusible tracer and therefore independent of the metabolic state of the tissue. The kinetic model of [^{15}O]H_2O is based on the assumptions that all activity is extracted by the parenchyma, extraction is very rapid, and tubular transport has not started or is insignificant at a level that does not influence the calculation of renal blood flow [10,11]. The [^{11}C]acetate has the same characteristics in the kidney, and has been used as a perfusion tracer in cardiac studies in human [5,12] and rats [13]. Still, net renal uptake of [^{11}C]acetate during the first 1 to 3 min after tracer injection is a reflection of both renal blood flow and first-pass extraction of acetate by renal tissue. Indeed, an estimate of actual renal blood flow can be computed from the derived K1 parameter using the relationship RBF = K1 × 1 / single pass extraction fraction. The single-pass renal extraction fraction of acetate in dogs based on one study is roughly 20 to 25% at baseline renal blood flow [6] while the exact renal extraction fraction of acetate in humans is not known. Using raw data, K1 values obtained were in line with previously published data [14] with baseline values ranging from 3 to 4.70 mL/min/g for [^{15}O] water and 1.15 to 2.33 mL/min/g for [^{11}C] acetate, a little bit lower. The difference between the two tracers could be explained by the extraction fraction of [^{11}C] acetate but this result should be confirmed by other studies.

Due to limited resolution of the PET, partial volume effect constitutes a limitation of any PET measure and needs to be taken into account to obtain quantitative measurements. While it is correct that ^{15}O has a longer positron range than ^{11}C, the difference in resolution is still well below the typical resolution of contemporary PET systems. ^{15}O and ^{11}C results in a ~3 mm and ~1 mm smoothing kernel to the final data, which is much less than a typical 5–7 mm kernel post-reconstruction filter and is not likely to contribute much to any differences therefore this correction was not applied. Estimation of renal extraction fraction of [^{11}C] acetate in humans was 50% at baseline RBF, as compared to 20 to 25% in dogs. Renal blood flow in dogs is a little bit lower compared to humans (1.94 ± 0.09 mL/min/g in mean) [15]. For all other blood flow tracers with sub-complete extraction, extraction is lowered at higher blood flow. Therefore, one can wonder if extraction fraction of acetate should not be <25% in humans at baseline. However, the extraction fraction in dogs is based on only one study by Shreve et al., therefore this result cannot be regarded as a certainty and those results need further validation to derive quantitative RBF measurements from [^{11}C] acetate data.

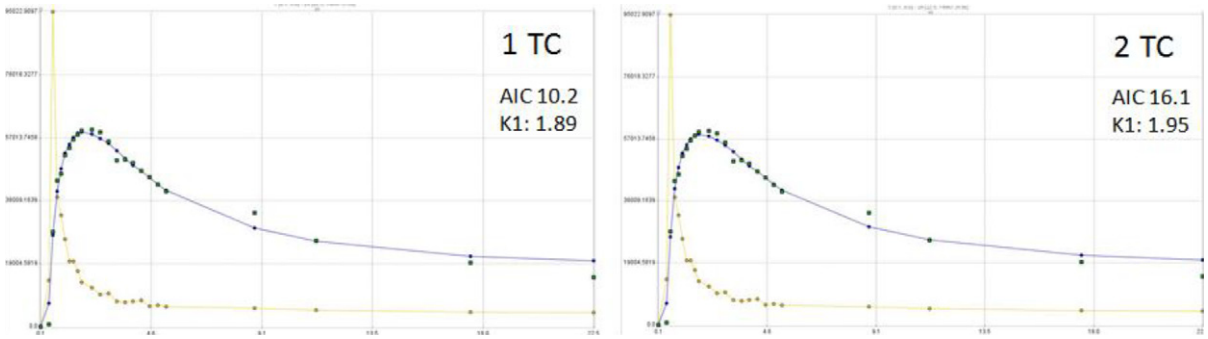

Fig. 1. Example of a sample time-activity curve and the 1T and 2T fit (+K1 and AIC values).

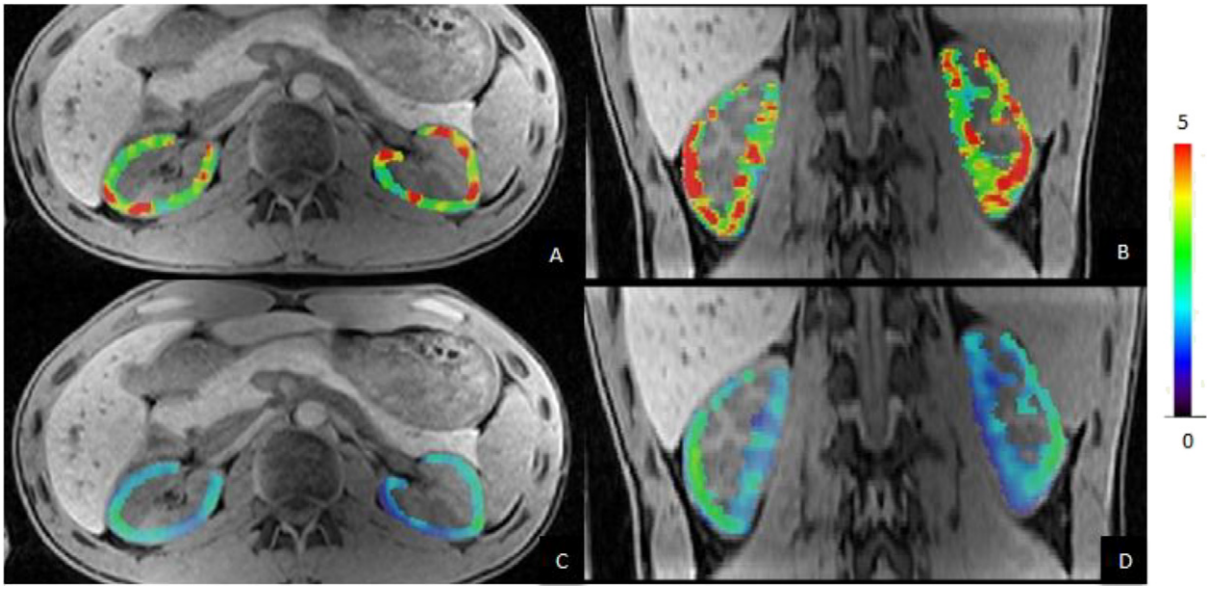

Fig. 2. Representative image of K1 for [^{11}C] Acetate and [^{15}O] water. (A) represents an axial view of [^{15}O]-water K1, (B) represents a coronal view of [^{15}O]-water K1, (C) represents an axial view of [^{11}C]-Acetate K1, (D) represents a coronal view of [^{11}C]-Acetate K1.

We used a PET/MR device for this study because we wanted to monitor tissue oxygenation using the MRI-BOLD technique (Blood Oxygen level dependent) after different protein loads but the comparison of [^{15}O]H_2O and [^{11}C]acetate data does not specifically require a PET/MR device as the latest PET/CT devices even have a higher resolution. Our results and the evaluation of RBF using [^{11}C] acetate can therefore be applied in the setting of a PET/CT scan.

This study has some limitations. First, it has been conducted in healthy subjects while both K1 and k2 are reduced in renal disease and renal artery stenosis [6], potentially limiting the applicability of our results to CKD patients. Second, we chose to compare renal perfusion obtained from [^{15}O]H_2O and [^{11}C]acetate from baseline evaluations only, because renal perfusion shows an important variability depending on study conditions. At baseline, our subjects were resting for >30 min, after an overnight fast, after a 48 hour low-protein diet to increase their comparability while post-protein loads evaluation conditions are less reproducible. Despite standardized conditions for baseline evaluation, our reproducibility parameters for [^{15}O] H_2O and [^{11}C]acetate are low and we cannot rule out that there are other day-to-day physiological factors affecting RBF that we did not control like cardiac output and that could account for our results. Third, net renal uptake of [^{11}C]acetate during the first 1 to 3 minute interval is dependent on tracer delivery and first-pass extraction of this tracer by the kidney, but the first-pass extraction probably varies inversely with flow rate as demonstrated in heart studies [16]. We did not measure the first-pass extraction but the close correlation between net [^{11}C]acetate uptake and renal blood flow using [^{15}O]H_2O, suggests that at baseline, the extraction fraction of [^{11}C]acetate does not vary enough to preclude this approach for indirectly assessing renal blood flow.

5. Conclusion

Using a PET/MR system, we were able to demonstrate that [^{11}C]acetate can be used as a perfusion tracer for kidney evaluation purposes. This result is notable because it allows to position [^{11}C]acetate as a 1st line PET tracer for renal perfusion evaluation. Quantitative evaluation of RBF from [^{11}C] acetate data would require a validation study to confirm the exact value of renal extraction fraction of [^{11}C]acetate in humans at different levels of RBF.

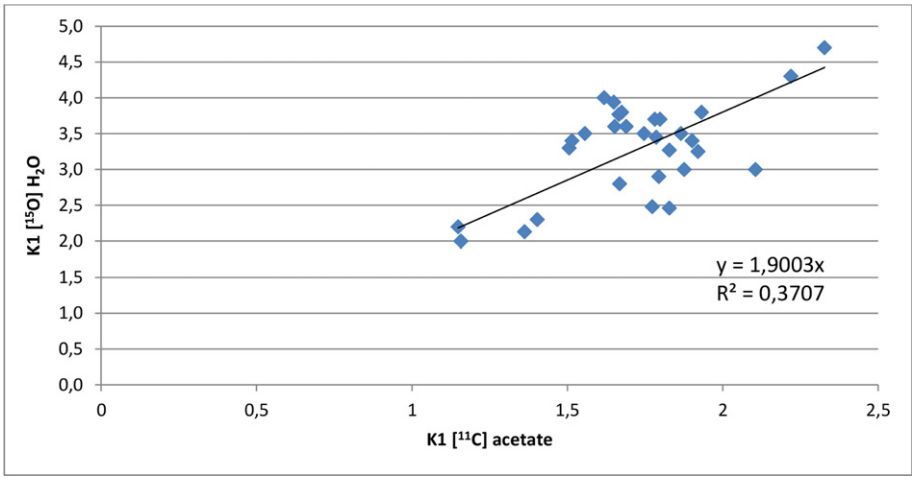

Fig. 3. Correlation between [^{11}C]-Acetate and [^{15}O]-water K1 values.

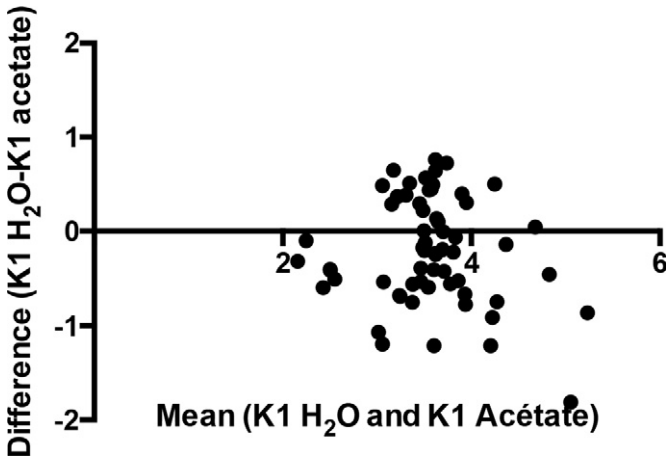

Fig. 4. Bland and Altman plot. Evaluation of the agreement between [^{11}C]-Acetate and [^{15}O]-water data sets.

Table 2
Reproducibility parameters of k1.

Acquisitions	Baseline	Typical error	ICC
^{15}O-H_2O	3.29 ± 0.65	0.36	0.64
^{11}C-acetate	1.73 ± 0.26	0.22	0.26
^{15}O-H_2O *vs* ^{11}C-acetate	–	0.37	0.43

6. Advances in knowledge and implications for patient care

We demonstrated that with a single injection of [^{11}C]acetate both renal oxidative metabolism and renal perfusion can be simultaneously assessed using a mono compartmental model, reducing patient irradiation, cost and study time and allowing a global evaluation of renal performances.

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Declaration of competing interest

The authors declare that no conflict of interest exists.

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