Am J Nucl Med Mol Imaging 2022;12(2):54-62
www.ajnmmi.us /ISSN:2160-8407/ajnmmi0143281

Original Article

Glomerular filtration rate calculation based on ^{68}Ga-EDTA dynamic renal PET

Ying Ding[1,2], Du Zhang[3], Min Wang[1,2], Li Zhang[1,2], Yu Liu[1,2], Yinqian Deng[1,2], Dawei Jiang[1,2], Yuqing Liu[4], Wei Cao[1,2]

[1]Department of Nuclear Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, Hubei, China; [2]Hubei Key Laboratory of Molecular Imaging, Wuhan 430022, Hubei, China; [3]School of Information Science and Technology, University of Science and Technology of China, Hefei 230026, China; [4]Institute of Artificial Intelligence, Hefei Comprehensive National Science Center, Hefei 230026, China

Received April 2, 2022; Accepted April 3, 2022; Epub April 15, 2022; Published April 30, 2022

Abstract: Positron emission tomography (PET) can accurately locate and quantify radioactivity over traditional single photon emission computed tomography (SPECT), encouraging its application in kidney function evaluation and glomerular filtration rate (GFR) measurement. ^{68}Ga-ethylenediamine-tetraacetic acid (^{68}Ga-EDTA) is a novel PET tracer for renal scan but a mature GFR calculation method still pending establishment. Herein, we aim to investigate the imaging performance of ^{68}Ga-EDTA dynamic PET in healthy C57BL/6 mice, establish quantitative methods to calculate GFR, and evaluate its feasibility in mice with kidney dysfunction. Dynamic PET of ^{68}Ga-EDTA successfully visualized the whole process of tracer elimination. GFR values were measured by the integral method (253.80±40.11 μL/min) and the Patlak Plot method (22.69±9.75 μL/min), while blood clearance rate of the tracer was found at 787.46±70.86 μL/min. The PET-based GFR values correlate well with the GFR_{blood} (R^2=0.7468, R^2=0.8793). The Integral method provides better accuracy than Patlak Plot method. Further application of GFR measurement in kidney-diseased mice proves better performance of the Integral method for defining split renal function.

Keywords: Glomerular filtration rate, PET/CT, Ga-68, EDTA, nuclear medicine

Introduction

Glomerular filtration rate (GFR) is the most important index of renal function while its direct measurement is complicated [1]. Single photon emission computed tomography (SPECT) using ^{99m}Tc-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) is the most widely used radioactive renal scanning method for precise GFR assessment in the clinic. Gate's method and its derived GFR measuring methods are mostly empirical, which assume that tracer filtration is completely through the glomerular thus we can estimate the total and individual kidney filtration from the radioactivity accumulated by each kidney during 120-180 sec after injection. However, the data obtained from SPECT renogram was only used to determine the renal accumulation of the tracer (in %ID) but not direct clearance rate, and many updated Gate's methods did not solve this issue [2]. Besides, limited by the low spatial resolution and semi-quantification properties of SPECT, single-photon measurements have to be corrected for tissue attenuation and kidney depth [3], which leads to GFR values questioned by clinicians.

Positron emission tomography (PET) imaging can achieve accurate spatial positioning and absolute quantification of radioactivity over traditional SPECT imaging [4]. The quantified radioactivity obtained through volumes of interest (VOIs) on PET images could well reflect the radioactivity concentrated in tissues. Thus, the renogram obtained through dynamic PET images can inform adequate information for GFR calculation, offering a more accurate means for non-invasive kidney function quantification. As previously reported [5-8], several studies verified that ^{68}Ga-EDTA (ethylenediaminetetraace-

tic acid) could be used for dynamic PET renal scanning. The metabolism of radioactivity that only filtrated through renal glomerular in vivo can be brought into the one-compartment pharmacokinetics model for calculation, setting the basis for GFR estimation [9-11]. However, this accuracy of this method requires further verification.

Here in our study, we performed ^{68}Ga-EDTA dynamic PET scanning on C57BL/6 mice, obtained renogram of mice for each kidney, and calculated GFR values using the integral method (GFR_{int}) as well as the Patlak Plot method (GFR_{Pat}), respectively. Two GFR values were further compared with ^{68}Ga-EDTA multi-sample blood clearance rate (GFR_{blood}). Furthermore, we performed ^{68}Ga-EDTA dynamic PET on mice with acute kidney injury (AKI) and unilateral ureteral obstruction (UUO), to verify the feasibility of PET-based GFR calculation methods and evaluate its application in split renal function assessment.

Methods

Materials

Chemicals were purchased from Aladdin Biochemical Technology Co., Ltd. (China) as reagent grade and used as received without further purification unless otherwise stated. ^{68}Ga was eluted from a ^{68}Ge/^{68}Ga-generator (ITG, Germany) with 0.05 M HCL as the eluent.

Tracer synthesis

^{68}Ga-EDTA was prepared by mixing 0.05 M EDTA (pH=8.0) and $^{68}GaCl_3$ at the molar ratio of 5000:1. The mixture was incubated at room temperature (26-28°C) for 10 min [12], and the final pH was adjusted to ~5 by adding 0.02 M sodium acetate buffer (pH=6.8). Radiochemical purity (RCP) of tracer was analyzed by instant thin-layer chromatography-silica gel (ITLC-SG) plates (Agilent Technologies, Inc, CA, USA), developed with a 0.2 M sodium acetate buffer (pH=4.5).

Animal experiment

Male C57BL/6 mice (8 weeks, 19-22 g) were purchased from Beijing SiPeiFu Bioscience Co., Ltd. (Beijing, China), housed at animal care facility of Hubei Province Key Laboratory of Molecular Imaging, reviewed and approved by the standards of the Institutional Animal Care and Use Committee of Tongji Medical College of Huazhong University of Science and Technology.

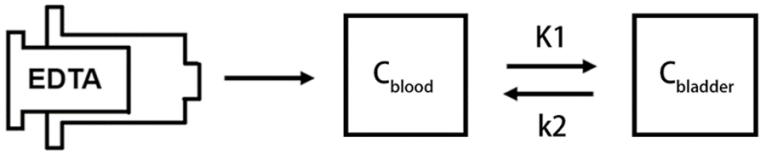
Mouse model of AKI was established after deprived water for 24 hours, 50% glycerol (8 ml/kg) was injected into each mouse's hind limb [5]. Mouse model of UUO was established by complete ligation of left ureter [13]. After operation, mice had to be observed carefully for at least 30 min. All mice were anesthetized with 2% isoflurane (RWD Life Science Co., Ltd., Shenzhen, China) for surgery and imaging. PET imaging was performed 24 hours after glycerol injection and ureteral ligation operation.

Dynamic PET renal scanning

PET scan was performed on Trans PET Discoverist 180, (RAYCAN Technology Co., Ltd., Suzhou, China). A cannula was inserted in the anesthetized mouse's tail vein. Then, the mouse was transferred to the scanner bed. A 30 min dynamic PET scan was performed in mouse, the tracer (3.82±0.95 MBq/100 μL) was administered as a bolus via the tail vein catheter concurrently with scan start, and a CT scan was followed after PET scan finished. The dynamic images were reconstructed using an ordered subset expectation maximization three-dimensional or maximum a posteriori (OSEM 3D/MAP) reconstruction algorithm and divided into 28 frames (10 s*6, 30 s*6, 60 s*6, 120 s*10). VOIs were defined on the heart left ventricle, kidneys, and bladder. Radioactivity within the VOIs of each frame was calculated and decay-corrected using Carimas (Finland). TACs were generated using the radioactivity within VOIs of each frame. Volume of kidney was calculated using PET image, and the region of interest (ROI) was manually drawn on each slide.

GFR measurement with ^{68}Ga-EDTA dynamic PET images

For the GFR_{PET} calculation, we employed one-compartment pharmacokinetics model to simulate the process of ^{68}Ga-EDTA elimination, used the Integral method and the Patlak Plot method to solve this kinetic model (**Figure 1**).



$$\text{Integral method: } \frac{dActivity_{bladder}(t)}{dt} = K_1 * Activity_{blood}(t)$$

$$\text{Patlak Plot method: } \frac{C_{kidney}(t)}{C_{plasma}(t)} = K_i * \frac{\int_0^t C_{plasma}(t)dt}{C_{plasma}(t)} + V$$

Figure 1. Diagram of the one-compartment pharmacokinetics model and the solving equations.

The Integral method: Based on one-compartment pharmacokinetics model, the change of tracer concentration in tissue can be expressed as $\frac{dC_{tissue}(t)}{dt}$, and the clearance rate of ^{68}Ga-EDTA could be solved using the equation below:

Eq. (1)

$$\frac{dActivity_{bladder}(t)}{dt} = Cl * Activity_{blood}(t)$$

Made the end time point at 30 min, and the Cl can be calculated using:

Eq. (2)

$$Cl = \frac{A_{bladder}(t)}{\int_{0\ min}^{30\ min} A_{blood}dt}$$

This method could only provide GFR value of bilateral kidneys but not for individual kidney. To obtain the split GFR value, we defined it equals to the ratio of single kidney area under curve (AUC) to total AUC at 2 to 3 min, and then multiplied the total GFR.

The Patlak Plot method: The Patlak Plot method is a specific graphic analysis method based on the compartment model to analyze the pharmacokinetics of tracer, of which regard the tissues that trapped tracer as a unity. The accumulation of tracer in VOI can be obtained from the equation below:

Eq. (3)

$$\frac{C_{kidney}(t)}{C_{blood}(t)} = K_i * \frac{\int_0^t C_{blood}(t)\,dt}{C_{blood}(t)} + V$$

K_i and V are the unknown constant that can be calculated by using linear regression form the plot of $\frac{C_{kidney}(t)}{C_{blood}(t)}$ against $\frac{\int_0^t C_{blood}(t)\,dt}{C_{blood}(t)}$. In our study, Ki was calculated at the time interval of 40-150 s.

And the split GFR is derived from K_i:

Eq. (4)

$$split\ GFR\ (\mu L/min) = K_i * Volume_{renal}$$

Input data of kidney should be adjusted by the Eq. (5):

Eq. (5)

$$C_{tissue}(t) = \frac{C_{PET}(t) - vB * C_{blood}(t)}{1 - vB}$$

The blood input data has to be adjusted by the Eq. (6):

Eq. (6)

$$C_{EDTA} = 0.39e^{-0.19t} + 1.17$$

GFR measurement with ^{68}Ga-EDTA multi-sample blood clearance

Blood samples (10 μl for each) were collected at 30 min, 60 min, and 120 min after tracer injection. Radioactivity was generated by γ counter (2470 Automatic Gamma Counter, WIZARD, PerkinElmer, Norwalk CT, USA). Results were decay corrected. The GFR was estimated by the one-compartment pharmacokinetics model and calculated by the following equation [10]:

Eq. (7)

$$GFR = \frac{injected\ dose}{AUC_{30\ min\ -\ 120\ min}}$$

Statistical analysis

Quantitative data are expressed as the mean ± standard deviation (SD). Differences among groups were compared using one-way ANOVA

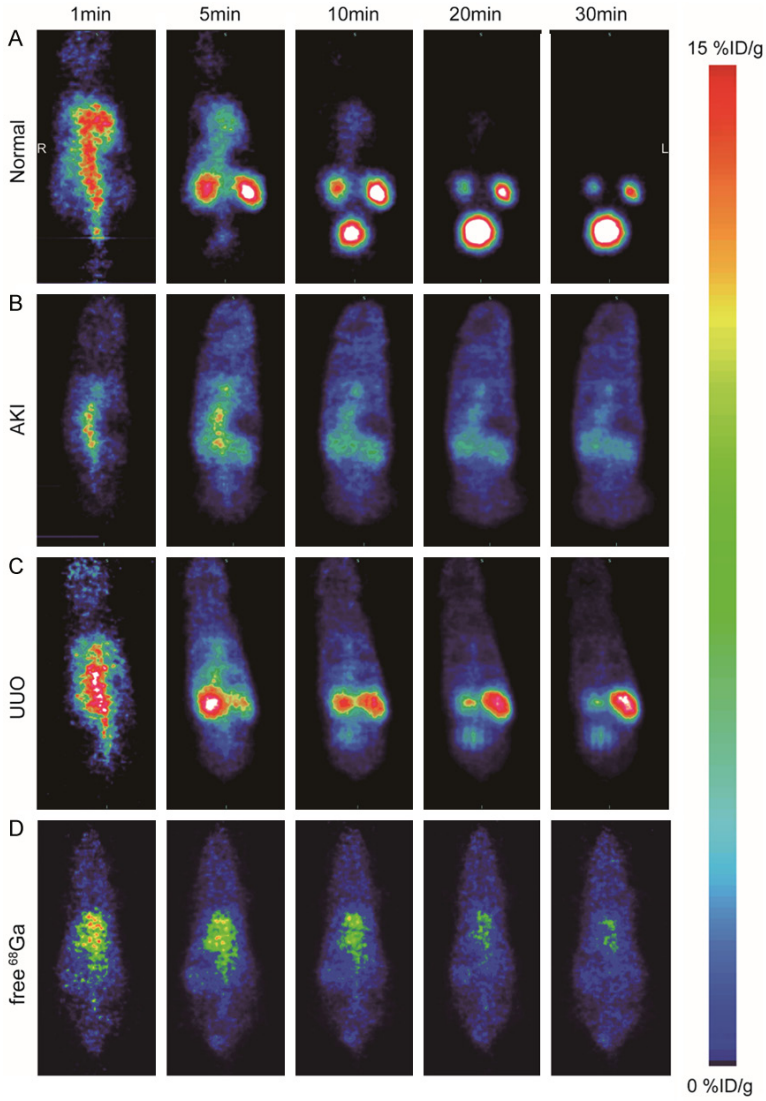


Figure 2. ^{68}Ga-EDTA dynamic PET/CT scanning at different time points postinjection. A. ^{68}Ga-EDTA dynamic PET/CT images performed in normal C57BL/6 mouse at 1 min, 5 min, 10 min, 20 min, 30 min p.i. B. ^{68}Ga-EDTA dynamic PET/CT images performed in AKI mouse. C. ^{68}Ga-EDTA dynamic PET/CT images performed in UUO mouse. D. Free ^{68}Ga dynamic PET/CT images performed in normal C57BL/6 mouse.

and students' *t* test. A *P* value of <0.05 was considered statistically significant. The linear regression and Pearson correlation test was performed for between-method agreements using Prism 7 (GraphPad Software, San Diego, CA).

Results

^{68}Ga-EDTA dynamic PET image

^{68}Ga-EDTA can be easily prepared at a high labelling efficiency (>99.0%). As shown in **Figure 2A**, after tracer injection into healthy mice, the tracer rapidly concentrated in the heart and eliminated through kidneys. Radioactivity was observed at kidneys within 1 min post injection. With the process of elimination, whole-body radioactive background reduced and ^{68}Ga-EDTA gathered in the bladder. There was no observed extrarenal elimination. On the contrary, free $^{68}Ga^{3+}$ *in vivo* circulates in the blood, rarely be eliminated through the kidneys within 30 min of injection (**Figure 2D**). TAC was plotted using the radioactivity from each frame in VOIs against time of each frame. ^{68}Ga-EDTA metabolism was fully visualized via PET imaging: after entering the blood pool, the tracer rapidly went through the kidneys for urinary elimination within a few mins of administration (**Figures 2A** and **3A**). At 1.5 min post injection, the radioactivity peaked at bilateral kidneys and all signal ended up in the bladder as time went by.

We also built AKI model and UUO model and performed ^{68}Ga-EDTA dynamic PET scanning. In AKI mice, eliminative ability of kidneys was damaged. After injecting ^{68}Ga-EDTA, radioactivity mainly stayed in the blood pool and the whole-body background signal was obviously higher than healthy mice. Kidney contour was highly blurred with diminished tracer retention when compared with healthy mice (**Figure 2B**). For kidneys, tracer uptake plateaued quickly after injection and little excretion can be found within 30 min of scanning (**Figure 3B** and **3E**). Half-maximal time ($T_{1/2}$) was used to define the excretion function of kidneys, and AKI mice did not reach $T_{1/2}$ within the time window of investigation (**Table 1**). As for UUO mice, after ligation of their left ureters, the obstructed kidney was

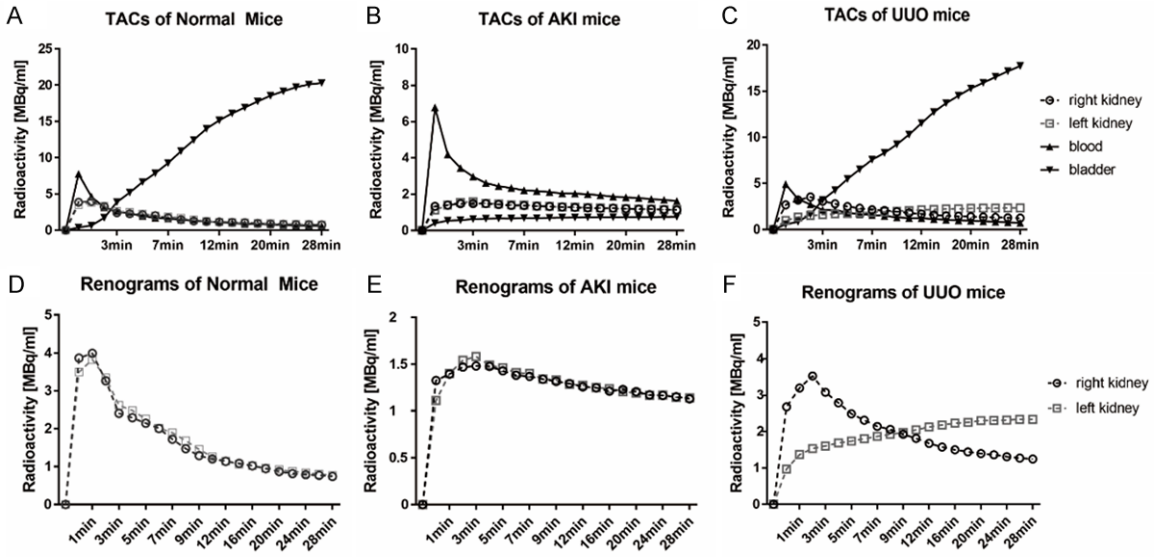


Figure 3. VOIs were put on the heart, bilateral kidneys and bladder, TACs were generated using the radioactivity in VOIs at each frame. TAC of each kidney was defined as the renogram. A. TACs of normal C57BL/6 mice. B. TACs of AKI mice. C. TACs of UUO mice. D. The renograms of normal C57BL/6 mice. E. The renograms of AKI mice. F. The renograms of UUO mice.

Table 1. GFR calculated by the integral method

Groups		peak value (MBq/mL)	T_{max} (min)	$T_{1/2}$ (min)	Ratio of $AUC_{2\text{-}3\ min}$	Split GFR (μL/min)	Total GFR (μL/min)
Control	R	46.64±3.41	2.17±0.58	8.67±2.31	50.4%	127.76±18.98	253.80±40.11
	L	38.29±2.73	1.50±0.00	8.33±1.53	49.6%	126.04±21.15	
AKI	R	16.47±1.48	3.00±0.87	/	49.1%	4.34±0.94	8.87±1.32
	L	16.09±3.45	3.17±2.02	/	50.9%	4.53±0.99	
UUO	R	37.62±17.65	2.50±1.00	14.00±5.29	69.8%	187.69±21.62	269.41±35.57
	L	/	/	/	30.2%	81.72±14.12	

still functional but could not excrete on Day 1 after surgery. The tracer radioactivity concentrated in the obstructed kidney and didn't decline as time passed by (**Figure 2C**), for which the renograms of obstructed kidney presented a continuous rising curve (**Figure 3F**). We further measured blood levels of creatinine (Cr) and urea nitrogen (BUN) in all groups and found that UUO mice had normal Cr and BUN levels as healthy mice, yet AKI animals showed significantly increased values, indicative of their damaged renal function (**Figure 4C** and **4F**).

PET-based GFR calculation using the integral method

Dynamic PET renogram was quantified directly by using Carimas which is automatically attenuated and corrected. When comparing with SPECT imaging, PET data did not need correction of renal depth or soft tissue, offering simplicity of calculation and improved data accuracy. Integral method was a classical analysis method for pharmacokinetics, which can be used to estimate drug clearance [10, 14]. GFR measurement using the integral method was calculated through the dose of tracer accumulated in the bladder dividing the sum of tracer concentrated in the blood during the period of scanning. This method employs data from the blood and the bladder TACs, and the result represents the total clearance rate of bilateral kidneys. The computed total GFR_{Int} of healthy C57BL/6 mice (n=3) was 253.80± 40.11 μL/min (**Figure 4A**). As shown in **Table 1** and **Figure 4D**, the defined split kidney GFR was 127.76±18.98 μL/min for the right kidney and 126.04±21.15 μL/min for the left. For AKI

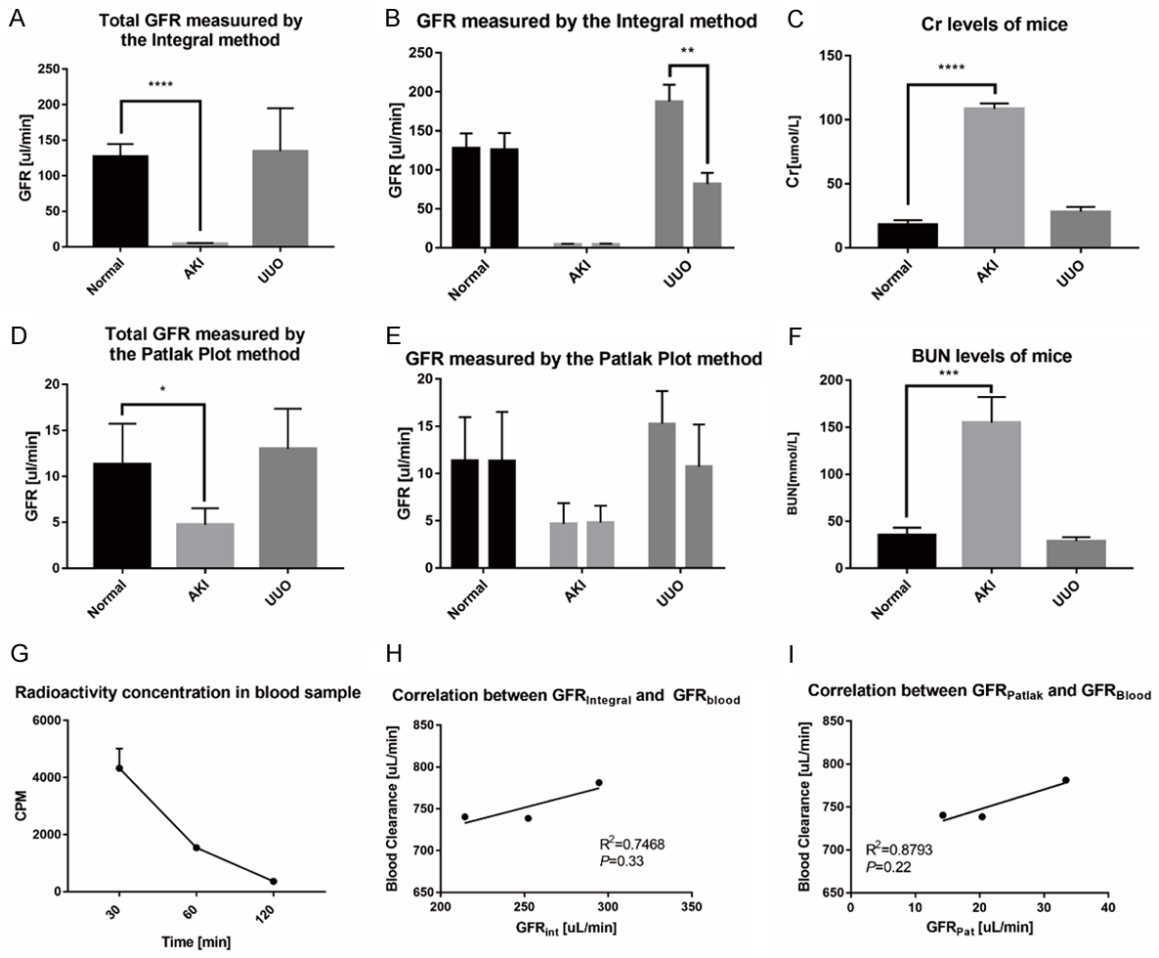


Figure 4. A. Total GFR measured by the Integral method, GFR of AKI mice was significantly lower than that of normal mice. B. The split GFR of each kidney measured by the Integral method, the GFR of UUO mice was of significant difference between the bilateral kidneys. C. The blood Cr values of different mice. D. Total GFR measured by the Patlak Plot method. E. The split GFR of each kidney measured by the Patlak Plot method. F. The BUN levels of different mice. G. The radioactivity concentration in each blood sample at each time point. H. The correlation between GFR measured by PET using the Integral method and the GFR measured by ^{68}Ga-EDTA blood clearance. I. The correlation between GFR measured by PET using the Patlak Plot method and the GFR measured by ^{68}Ga-EDTA blood clearance. (*P<0.05, **P<0.01, ***P<0.001, ****P<0.0001).

mice, the total GFR_{int} was 8.87±1.32 μL/min, while 4.34±0.94 μL/min and 4.53±0.99 μL/min was calculated for the right and left kidney, respectively. For UUO mice, the tracer elimination of the unligated kidney was slightly slower than normal kidneys (14.00±5.29 min vs 8.50±1.76 min) (**Table 1**), but in general, the total GFR_{int} (269.41±35.57 μL/min) was consistent with values measured from healthy mice (**Figure 4A**). These measurements correlated well with our observation from PET imaging and previous reports (200-300 μL/min) [15-17]. As to the split GFR, unligated GFR_{int} was measured at 187.69±21.62 μL/min while the obstructed kidney GFR_{int} was 81.72±14.12 μL/min. The overestimation of the ligated kidney elimination suggests that the integral method will overweight the blood perfusion in the obstructed kidneys, leading to biased values for split kidney function quantification.

PET-based GFR calculation using the Patlak Plot method

The Patlak Plot method is a graphic analysis method which uses the linear regression to fit the slope (K_i) of Patlak graph [18, 19]. This simple method calculates clearance rate (K_i) for each kidney directly by using the tracer concentration data in the blood and kidneys. The overall GFR_{Pat}, right kidney GFR and left kidney GFR of healthy mice was 22.69±9.75 μL/min,

Table 2. GFR calculated by the Patlak Plot method

Groups		Ki (mL/cm^3*min)	Kidney Volume (mm^3)	Split GFR (μL/min)	Total GFR (μL/min)
Control	R	0.0377±0.0140	300.17±18.17	11.37±4.58	22.69±9.75
	L	0.0374±0.0153	299.97±18.26	11.32±5.17	
AKI	R	0.0236±0.0108	198.60±22.13	4.67±2.19	9.48±3.89
	L	0.0244±0.0079	195.60±21.93	4.80±1.77	
UUO	R	0.0506±0.0102	301.03±7.42	15.27±3.46	25.99±6.57
	L	0.0294±0.0097	356.13±48.75	10.72±4.49	

11.37±4.58 μL/min and 11.32±5.17 μL/min, respectively. And the total GFR_{Pat} of AKI mice was 9.48±3.89 μL/min. Split kidney GFR for the right and the left was 4.67±2.19 μL/min and 4.80±1.77 μL/min. As to UUO mice, the GFR_{Pat} of total, right and left was 25.99±6.57 μL/min, 15.27±3.46 μL/min, and 10.72±4.49 μL/min, respectively. K_i was calculated as the slope of plot between 40-150 s after tracer injection, which made this method mainly affected by blood perfusion. Thus, the Patlak Plot method also overestimated the function of the obstructed kidney in UUO mice (**Figure 4E**). The results of GFR_{Pat} were obviously lower than those measured by GFR_{int}, which was attributed to systematical underestimation of kidney elimination of this method (**Table 2** and **Figure 4D**).

GFR_{EDTA} of the blood clearance measured by multi-sample method

Estimation of tracer blood clearance was measured to further validate the accuracy of GFR values obtained from PET imaging. Blood samples were collected at 30 min, 60 min and 120 min from each group and measured the radioactivity by using γ counter (**Figure 4G**). To our satisfaction, the results were found more consistent with valued from the integral method with the GFR_{blood} in healthy mice as 787.46±70.86 μL/min.

Discussion

As previous reported [7, 20], ^{68}Ga-EDTA has low blood protein binding rate and its blood clearance was close to FITC-inulin blood clearance in rats, encouraging us to employ this tracer for kidney function evaluation. Previous reports showed that dynamic PET imaging using ^{68}Ga-EDTA is a highly efficient means to visualize kidney elimination, but its quantification may bring more benefits for split renal function evaluation in clinical settings [5]. Thus, we bring the GFR calculation to completion in this study using simple but classical pharmacokinetic model based on ^{68}Ga-EDTA nuclear imaging. We found that the GFR values of normal C57BL/6 mice were measured at 253.80± 40.11 μL/min and 22.69±9.75 μL/min by using the integral method and the Patlak Plot method, respectively. Patlak Plot method underestimates kidney excretion due to down-regulation of the K_i value during calculation. Besides, the ^{68}Ga-EDTA blood clearance rate was 787.46±70.86 μL/min, consistent with the GFR_{int}. Thus, we consider integral method more suitable for GFR measurement, and suits well for defining GFR values in models of kidney dysfunction, including AKI mice and UUO mice in this study.

FITC-inulin blood or urine clearance tests are the gold standard for GFR determination in the clinic [21]. However, the total blood volume of mice that could be collected was approximately 2 mL, which limits the measurement of FITC-inulin blood clearance and multiple blood collection increases risk of animal loss. Moreover, blood or urine tests could not inform split renal function. PET imaging offers high sensitivity, improved quantification, and ease of operation, which has the potential to become the mainstream method. Measuring GFR by PET imaging provides a visual evaluation of mouse renal function and distinguishes bilateral kidneys at the same time, while keeping all animals alive before and after animal model establishment.

Our study confirmed the value of ^{68}Ga-EDTA dynamic PET scanning in mouse renal function evaluation and GFR determination using two quantification methods. In our study, GFR_{int} of C57BL/6 mice was in accordance to previous reports at 200-300 μL/min [22], GFR_{int} of diseased mice was also as expected within 30 min of scanning time. Tracer blood clearance was

further calculated between 30-120 min to verify the accuracy of PET-based measurements. GFR_{blood} was higher than PET-based GFR, because the injection dose was obviously bigger when compared with the radioactivity accumulated in the bladder at 30 min post injection. Besides, Patlak Plot method was another method often used to assess kidney function. Our results showed its effectiveness in analyzing kidney function, but the calculated values are one order of magnitude lower than GFR_{int}. In the integral method calculation, GFR is defined as the clearance rate of ^{68}Ga-EDTA from blood to urine but not the tracer clearance within the glomerular, which will give rise the calculated GFR value [23]. Despite that, GFR_{Pat} values have great agreement with GFR_{blood} in healthy mice (**Figure 4I**). Many factors had to be taken into account for GFR calculation, including the estimate of tracer volume of distribution (Vd) and the time to reach equilibrium distribution. For PET imaging-based GFR calculation, blood and plasma signal also influences the result.

^{68}Ga-EDTA dynamic renal PET image well reflected the tracer elimination process within 30 min of scanning time, obtained accurate kidney location, visualized the change of renal function in diseased kidneys, and identified abnormal anatomy. The appropriate decay half-life (68 min) and radioactive energy of ^{68}Ga permit repeated PET imaging of the same group of animals within a short interval. Thus, ^{68}Ga-EDTA dynamic renal PET is the most practical method for renal function evaluation in mice, and has great opportunity to extend its use on human beings. The integral method is a classic method to estimate elimination kinetics, which performed well at PET image-based mice GFR calculation. The calculated GFR is highly consistent with reported values in healthy C57BL/6 mice and has great agreement with GFR_{blood}. Moreover, the calculation equation is simple and easy to implement. However, our study had certain limitations. The number of mice was limited. Besides, hydration status of mice would affect the clearance rate of tracer in kidneys, which was difficult to control and unified.

Conclusion

In summary, with the establishment of ^{68}Ga-EDTA dynamic PET scanning, and the accomplishment of PET-based pharmacokinetic analyze in healthy C57BL/6 mice and renal disease model, we proved ^{68}Ga-EDTA dynamic PET is a stable and convenient method for mice renal function evaluation. ^{68}Ga-EDTA PET image present the process of tracer elimination in kidney completely. The PET-based integral method is suitable for quantifying mice renal function, and the calculated GFR of mice was with high accuracy.

Acknowledgements

This study was financially supported by the National Key Research and Development Program of China (No. 2017YFC0113302), the National Natural Science Foundation of China (82102121), National R&D Program for Major Research Instruments of Natural Science Foundation of China (61927801) and the opening foundation of Hubei key laboratory of molecular imaging (2020fzyx023). The authors also thank Dr. Qingguo Xie of the School of Life Science and Technology, Huazhong University of Science and Technology, for his kind help in acquisition of images using the small-animal PET scanner.

Disclosure of conflict of interest

None.

Address correspondence to: Yuqing Liu, Institute of Artificial Intelligence, Hefei Comprehensive National Science Center, Hefei 230026, China. E-mail: yqliu@iai.ustc.edu.cn; Wei Cao, Department of Nuclear Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, Hubei, China. E-mail: caowei@hust.edu.cn

References

[1] Stevens LA and Levey AS. Measured GFR as a confirmatory test for estimated GFR. J Am Soc Nephrol 2009; 20: 2305-2313.

[2] Kang YK, Park S, Suh MS, Byun SS, Chae DW and Lee WW. Quantitative single-photon emission computed tomography/computed tomography for glomerular filtration rate measurement. Nucl Med Mol Imaging 2017; 51: 338-346.

[3] Xue J, Deng H, Jia X, Wang Y, Lu X, Ding X, Li Q and Yang A. Establishing a new formula for estimating renal depth in a Chinese adult population. Medicine (Baltimore) 2017; 96: e5940.

[4] Rosar F, Pauly P, Ries M, Schaefer-Schuler A, Maus S, Schreckenberger M, Khreish F and Ezziddin S. Determination of split renal function

by PSMA imaging: comparison of 68Ga-PSMA-11 PET with 99mTc-MAG3 scintigraphy. Am J Nucl Med Mol Imaging 2020; 10: 249.

[5] Ni D, Jiang D, Kutyreff CJ, Lai J, Yan Y, Barnhart TE, Yu B, Im HJ, Kang L, Cho SY, Liu Z, Huang P, Engle JW and Cai W. Molybdenum-based nanoclusters act as antioxidants and ameliorate acute kidney injury in mice. Nat Commun 2018; 9: 1-11.

[6] Hofman M, Binns D, Johnston V, Siva S, Thompson M, Eu P, Collins M and Hicks RJ. ^{68}Ga-EDTA PET/CT imaging and plasma clearance for glomerular filtration rate quantification: comparison to conventional 51Cr-EDTA. J Nucl Med 2015; 56: 405-409.

[7] Gündel D, Pohle U, Prell E, Odparlik A and Thews O. Assessing glomerular filtration in small animals using [68Ga] DTPA and [68Ga] EDTA with PET imaging. Mol Imaging Biol 2018; 20: 457-464.

[8] Fontana AO, Melo MG, Allenbach G, Georgantas C, Wang R, Braissant O, Barbey F, Prior JO, Ballhausen D and Viertl D. The use of 68Ga-EDTA PET allows detecting progressive decline of renal function in rats. Am J Nucl Med Mol Imaging 2021; 11: 519.

[9] Chang J, Ahn S, Choi S, Lee H, Chang D, Choi H and Lee Y. Evaluation of glomerular filtration rate by use of dynamic computed tomography and Patlak analysis in clinically normal cats. Am J Vet Res 2011; 72: 1276-1282.

[10] Hackstein N, Wiegand C, Langheinrich A and Rau WS. Measurement of glomerular filtration rate by low-dose iopromide plasma clearance. Acta Radiol 2003; 44: 162-165.

[11] Gaspari F, Perico N and Remuzzi G. Application of newer clearance techniques for the determination of glomerular filtration rate. Curr Opin Nephrol Hypertens 1998; 7: 675-680.

[12] Jiang D, Ge Z, Im HJ, England CG, Ni D, Hou J, Zhang L, Kutyreff CJ, Yan Y, Liu Y, Cho SY, Engle JW, Shi J, Huang P, Fan C, Yan H and Cai W. DNA origami nanostructures can exhibit preferential renal uptake and alleviate acute kidney injury. Nat Biomed Eng 2018; 2: 865-877.

[13] Jiang D, Im HJ, Boleyn ME, England CG, Ni D, Kang L, Engle JW, Huang P, Lan X and Cai W. Efficient renal clearance of DNA tetrahedron nanoparticles enables quantitative evaluation of kidney function. Nano Res 2019; 12: 637-642.

[14] Schnöckel U, Reuter S, Stegger L, Schlatter E, Schäfers KP, Hermann S, Schober O, Gabriëls G and Schäfers M. Dynamic 18F-fluoride small animal PET to noninvasively assess renal function in rats. Eur J Nucl Med Mol Imaging 2008; 35: 2267-2274.

[15] Werner RA, Wakabayashi H, Chen X, Hirano M, Shinaji T, Lapa C, Rowe SP, Javadi MS and Higuchi T. Functional renal imaging with 2-deoxy-2-18F-fluorosorbitol PET in rat models of renal disorders. J Nucl Med 2018; 59: 828-832.

[16] Wang W, Jittikanont S, Falk SA, Li P, Feng L, Gengaro PE, Poole BD, Bowler RP, Day BJ, Crapo JD and Schrier RW. Interaction among nitric oxide, reactive oxygen species, and antioxidants during endotoxemia-related acute renal failure. Am J Physiol Renal Physiol 2003; 284: F532-F537.

[17] Cochrane AL, Kett MM, Samuel CS, Campanale NV, Anderson WP, Hume DA, Little MH, Bertram JF and Ricardo SD. Renal structural and functional repair in a mouse model of reversal of ureteral obstruction. J Am Soc Nephrol 2005; 16: 3623-3630.

[18] Hackstein N, Kooijman H, Tomaselli S and Rau WS. Glomerular filtration rate measured using the Patlak plot technique and contrast-enhanced dynamic MRI with different amounts of gadolinium-DTPA. J Magn Reson Imaging 2005; 22: 406-414.

[19] Hackstein N, Heckrodt J and Rau WS. Measurement of single-kidney glomerular filtration rate using a contrast-enhanced dynamic gradient-echo sequence and the Rutland-Patlak plot technique. J Magn Reson Imaging 2003; 18: 714-725.

[20] Lee JY, Jeong JM, Kim YJ, Jeong HJ, Lee YS, Lee DS and Chung JK. Preparation of Ga-68-NOTA as a renal PET agent and feasibility tests in mice. Nucl Med Biol 2014; 41: 210-215.

[21] National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002; 39 Suppl 1: S1-266.

[22] Qi Z, Whitt I, Mehta A, Jin J, Zhao M, Harris RC, Fogo AB and Breyer MD. Serial determination of glomerular filtration rate in conscious mice using FITC-inulin clearance. Am J Physiol Renal Physiol 2004; 286: F590-F596.

[23] Katayama R, Yamaguchi N, Yamashita T, Watanabe S, Satoh H, Yamagishi N and Furuhama K. Calculation of glomerular filtration rate in conscious rats by the use of a bolus injection of iodixanol and a single blood sample. J Pharmacol Toxicol Methods 2010; 61: 59-64.