

Comparison between Three Techniques for Determining Glomerular Filtration Rates: ^{99m}Tc -Diethylene Triamine Penta-Acetic Acid Renography, Double Plasma Sampling Method, and Single Plasma Sampling Method in Vietnamese Patients

Abstract

Glomerular filtration rate (GFR) is an important indicator of renal function. Many methods have been developed to determine GFR in clinical examinations. This study aims to correlate between radionuclide plasma sampling methods (single and double blood samples, *in vitro* methods) and *in vivo* Gate's method using ^{99m}Tc -diethylene triamine penta-acetic acid (^{99m}Tc -DTPA) renography.

Materials and Methods: 43 patients underwent this study, including 31 renal donors (Group 1) and 12 patients with obstructive uropathy (Group 2). All patients were administered with a range of 5–7 mCi of ^{99m}Tc -DTPA. Then, renography performed simultaneously after injection and GFR calculation followed by Gate's method. Blood samples were collected at 60- and 120-min postinjection, samples were counted by a thyroid uptake system, and GFR was calculated using a single plasma sample method (SPSM) and a double plasma sample method (DPSM). **Results:** The mean GFRs calculated by Gate's method in Groups 1 and 2 were 85.8 ± 18.2 ml/min and 118.4 ± 13.9 ml/min, respectively. Meanwhile, using the *in vitro* blood sampling methods (DPSM and SPSM), the mean GFRs in Group 1 were 73.8 ± 15.4 ml/min and 56.4 ± 20.9 ml/min, respectively, and in Group 2 were 116.8 ± 12.9 ml/min and 106.3 ± 18.5 ml/min, respectively. There is a high correlation between Gate's method and DPSM in two groups ($r = 0.86$ and 0.72 , respectively), and a moderate correlation was found between Gate's method and SPSM in both groups ($r = 0.49$ and $r = 0.37$, respectively). The two *in vitro* methods (DPSM and SPSM) revealed that moderate correlation in both groups ($r = 0.74$ and $r = 0.67$, respectively) was observed. **Conclusion:** Renography is a simple method but considered inaccurate for GFR determination. However, *in vitro* plasma sampling is rarely used in Vietnam. In this study, Gate's method correlated well with DPSM and tended to overestimate GFR. Further, the *in vitro* methods can be applied to correct the *in vivo* method as a confirmatory test in some cases.

Keywords: Gates, glomerular filtration rate, plasma sample method, renography, Tc-^{99m} diethylene triamine penta-acetic acid

Introduction

Glomerular filtration rate (GFR) describes the flow rate of fluid filtered from glomerulus to Bowman's space per time unit and plays an important role in the evaluation of renal function. Inulin clearance is widely accepted as a golden standard method for the determination of GFR.^[1] However, this method requires a complex technique and is time-consuming; therefore, it is considered to be difficult for routine clinical practice. By using some radiopharmaceuticals that have the same properties as inulin and could be measured, the filtration rate could be calculated easier.

In Europe, ^{51}Cr -ethylene diamine triacetic acid (^{51}Cr -EDTA) is recommended as a standard radiopharmaceutical for GFR measurement, while ^{99m}Tc -diethylene triamine pentaacetic acid (^{99m}Tc -DTPA) and ^{125}I -iothalamate are more prevalent in the US. Initially, a time-activity curve stimulating renal excretion was created from multiple plasma samples, but it was found difficult to perform. Therefore, several modified methods are proposed in which only one or two blood samples are required.^[2–4]

Gamma camera-based ^{99m}Tc -DTPA renography is a noninvasive technique that

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does not require blood or urine samples. Renography could determine split renal function while others only calculate global function.^[5] Nevertheless, its main disadvantages include radioisotopes safety, experience expertise, and debatable level of precision.

In Vietnam, *in vivo* method renal scintigraphy is popular for GFR evaluation, but *in vitro* methods are not. Our study aims to compare these methods for correlation and concordance and in some circumstances *in vitro* methods could be applied as the confirmatory test for Vietnamese patients.

Materials and Methods

From January 2019 to June 2019, we collected results from 43 subjects (17 females and 26 males) and separated them into two groups: 31 renal donors (Group 1) and 12 patients diagnosed with obstructive uropathy (Group 2). All patients were sent for routine renal study in the nuclear medicine department in our hospitals. Informed consent forms were given to all patients.

Renography (Gate's method)

Patients were well hydrated with 500 ml of water before the test. ^{99m}Tc-DTPA was prepared in our hot laboratory using a commercial cold-kit (Pentacis, Curium, France); quality control by thin-layer chromatography was applied after radio-labeling to assure radiochemistry purities not <95%. A preinjection syringe containing doses from 185 to 260 MBq (5–7 mCi) was counted by a dual-head gamma camera (GE-Discovery). The patients were laid down on the bed in a supine position and ^{99m}Tc-DTPA was given intravenously and flushed by 20 ml of saline. Posterior dynamic images (1 frame per 2 s for 60 s in perfusion phase and followed by 1 frame per 2 min for 30 min in function phase) were obtained in a 128 × 128 matrix and low-energy high-resolution collimator. Activity in the postinjection syringe was measured using the gamma camera. Region of interests (ROIs) for each kidney, cortex region, background, and aorta were drawn manually, and the time–activity curve was generated by Xeleris software (GE, USA). GFR was calculated automatically according to the Gate's algorithm^[6] and was normalized for a body surface area (BSA) of 1.73 m².

In vitro plasma sampling methods (double plasma sampling method and single plasma sampling method)

Residual radioactivity in the postinjected syringe was counted by a dose calibrator. When renal scintigraphy was finished, the first blood sample (about 10 ml) was collected intravenously from the opposite arm to prevent radiation contamination at 60-min postinjection, and the second one was taken at 120-min postinjection. The blood samples were centrifuged at 10,000 rpm for 10 min to separate plasma and red blood cells. A standard solution was prepared by diluting the same amount of

^{99m}Tc-DTPA (5–7 mCi) radioactivity in 1000 ml water. Then, 1 ml of plasma samples and standard solution were counted in a thyroid uptake system (Atomlab 960, Biodex, USA) for 1 min. 60-min and 120-min plasma samples were used for DPSM and 120-min samples were used for SPSM. Radioactivity decay was corrected and GFR was calculated by using the following formulas:

Single plasma sampling method

$$\text{GFR} = A \times \ln\left(\frac{D}{P}\right) + B$$

where D = dose (counts/min), P = plasma activity (counts/min-ml), and T = time between injection and withdrawing of sample (min)

$$A = -0.27T + 119.1 + 2405/T$$

$$B = 2.866T - 1222.9 - 16,820/T$$

GFR is in ml/min.

Double plasma sampling method

$$\text{GFR} = \left[\frac{D \times \ln\left(\frac{P_1}{P_2}\right)}{T_2 - T_1} \exp\left(\frac{(T_1 \ln(P_2)) - (T_2 \ln(P_1))}{T_2 - T_1}\right) \right]^{0.979}$$

where D = dose (counts/min), P₁ = plasma activity at time T₁ (counts/min-ml), P₂ = plasma activity at time T₂ (counts/min-ml), and GFR is in ml/min.

These formulas were following Russell's method.^[7] The final result was also normalized for BSA of 1.73 m² due to Haycock *et al.*^[8]

where BSA in m², weight in kg, and height in cm.

Statistical methods

All statistical calculations were performed by SPSS program (Statistical Package for the Social Science) version 26 and Microsoft Excel 365 for Mac OS. Data were presented as the mean ± standard deviation. For methods comparison, linear correlation, coefficient, and paired *t*-test were performed.

Results

Forty-three patients, including 17 females and 26 males, participated in the study and were divided into two groups. GFR means in Group 1 measured by renography, DPSM, and SPSM were 85.8 ± 18.2 ml/min/1.73 m², 73.8 ± 15.4 ml/min/1.73 m², and 56.4 ± 20.9 ml/min/1.73 m², respectively. Meanwhile, in Group 2, the GFR means using renography, DPSM, and SPSM were 118.4 ± 13.9 ml/min/1.73 m², 116.8 ± 12.9 ml/min/1.73 m², and 106.3 ± 18.5 ml/min/1.73 m², respectively. The difference in mean values was statistically significant between two groups (*P* < 0.01) [Table 1].

The difference in mean values between Gate's method and DPSM in Group 1 was statistically significant (*P* < 0.01).

A statistically significant difference was also found between mean GFR values using *in vitro* DPSM and SPSM in Group 1 ($P < 0.01$). However, in Group 2, no significant difference was found between mean GFR values measured by *in vivo* renal scintigraphy and *in vitro* DPSM, which were 118.4 ± 13.9 ml/min/1.73 m² and 116.8 ± 12.9 ml/min/1.73 m², respectively ($P = 0.37$). By contrast, there were statistically significant differences when comparing mean values of GFR between SPSM with Gate's method and DPSM in Group 2 ($P < 0.01$).

A highly significant correlation was found between *in vitro* DPSM and *in vivo* Gate's method in both groups, $r = 0.86$ for Group 1 and $r = 0.72$ for Group 2 [Figure 1]. There is a low correlation between renography and *in vitro* SPSM in both groups ($r = 0.49$ and 0.37). Group 1 and Group 2 also showed a moderate correlation when compared between two radionuclide methods ($r = 0.74$ and 0.67 , respectively).

The Bland and Altman's analysis for the global difference in the GFR (DPSM–Gate) and (SPSM–Gate) showed a mean value of -4.54 ± 10.88 ml/min/1.73 m² (confident interval [CI] 95%: -7.88 to -1.19) and -17.06 ± 18.44 ml/min/1.73 m² (CI 95%: -22.73 to -11.38) [Figure 2].

Discussion

GFR is one of the most important indexes for renal function assessment. Many methods are currently used and developed for estimating GFR to improve accuracy and optimize procedures, including serum creatinine-based or serum cystatin-based equations and renal radiopharmaceutical-based methods.^[9,10] ^{99m}Tc-DTPA or ⁵¹Cr-EDTA or ¹²⁵I-iothalamate are the most commonly used radiopharmaceuticals for GFR measurement. They have shown a high correlation with inulin renal clearance which is the gold standard method.

Table 1: Means and ranges of glomerular filtration rate measured by *in vivo* and *in vitro* methods

Methods	Group 1 (n=12)		Group 2 (n=31)		t-test	
	Range	Mean±SD	Range	Mean±SD	t	P
Gate	51.0108.1	85.8±18.2	84.2143.3	118.4±13.9	-5.6	<0.01
DPSM	43.995.2	73.8±15.4	97.4140.2	116.8±12.9	-8.6	<0.01
SPSM	13.078.4	56.4±20.9	77.9159.2	106.3±18.5	-7.2	<0.01

SD: Standard deviation, DPSM: Double plasma sample method, SPSM: Single plasma sample method

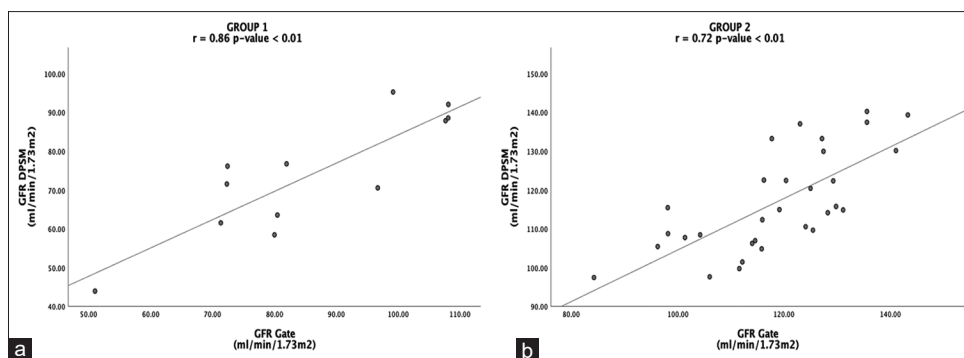


Figure 1: Scatter plots of glomerular filtration rate estimated by double plasma sampling method against that by Gate's method in Group 1 (a) and Group 2 (b). The lines indicate the regression

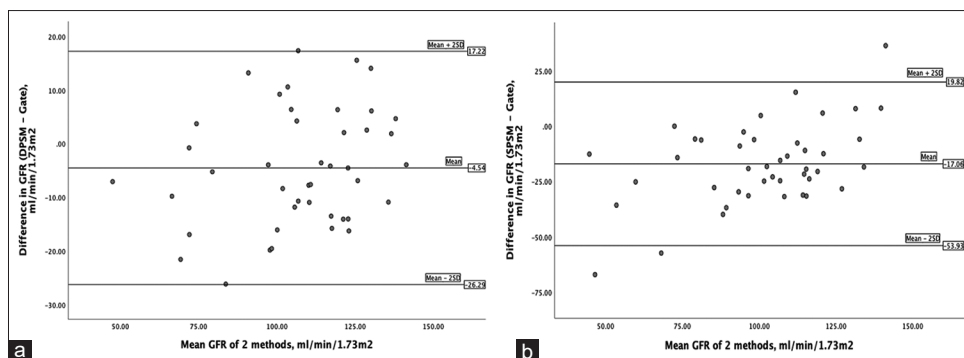


Figure 2: Bland and Altman plots of difference in glomerular filtration rate by double sampling method (a) and single sampling method (b) against Gate's method. The solid lines indicate the mean difference and 95% of agreement (2 standard deviation)

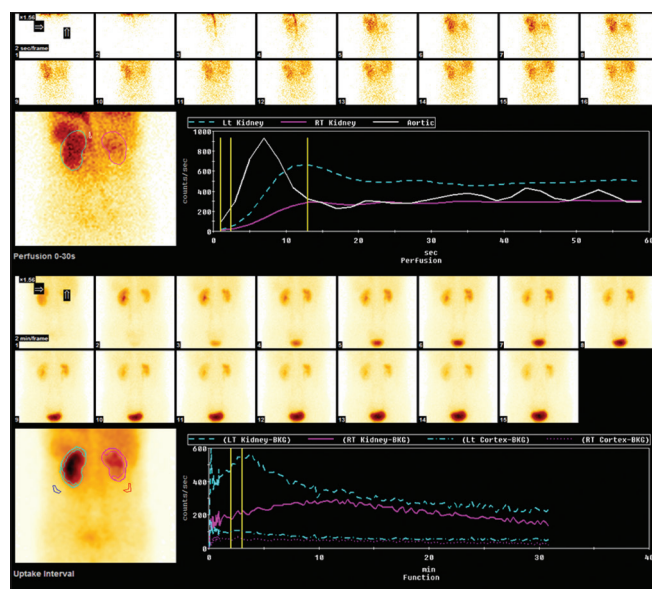


Figure 3: Renal scintigraphy with perfusion graph and function graph for glomerular filtration rate evaluation

Gate's method or renal scintigraphy and serum creatinine method are more common methods for GFR estimation than *in vitro* plasma methods in Vietnam [Figure 3]. However, their accuracy is arguable and considered less reliable than plasma sampling methods.

The results demonstrated that the DPSM correlated well with the Gate's method in both groups ($r = 0.86$ and 0.72). This DPSM using Russell's formula is a reliable method for the valid determination of the true GFR.^[11,12] However, SPSM presented a moderate correlation with DPSM and renography, which might be caused by using the second 120-min plasma sample which should be collected at 180-min postinjection, and it might cause erroneous. Multiple sampling methods are inconvenient for patients, and in practice, patients whose GFR are less than 45 ml/min are recommended to use DPSM.^[13]

Bland and Altman analysis showed that *in vivo* GFR measured by Gate tended to overestimate the value obtained from *in vitro* methods with the mean difference of -4.54 and -17.06 ml/min/1.73 m². Similar results were reported in a study by Itoh *et al.*^[2]

Conclusion

In conclusion, Gate's method or renography presented a simple way to evaluate global glomerular filtration as well as general comparison of renal function between two kidneys, which is important in the case of a kidney transplant. The accuracy of this method is currently studied and improved in our hospitals, especially in patients with very low GFR or children, in which plasma sampling methods are recommended. Even though the application

of three methods for GFR has been reported, this report provides the first comparison of their application for people from Southeast Asian countries.

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Conflicts of interest

There are no conflicts of interest.

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