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Comparison of methods for determination of glomerular filtration rate: Tc-99m-DTPA renography, predicted creatinine clearance method and plasma sample method

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Background: The gamma camera uptake method with Tc-99m-DTPA is simple and less time consuming for the determination of the glomerular filtration rate (GFR). However, its diagnostic accuracy is debated. Gates' method and predicted creatinine clearance method were compared with plasma clearance method with Tc-99m-DTPA for the measurement of GFR. ***Materials and Methods:*** Tc-99m-DTPA renography was performed on 133 patients (69 males and 64 females; age range being 24 to 84 years) with a wide range of renal function. The GFR was determined simultaneously by 3 methods; (1) gamma camera uptake method (modified Gates, Gates); (2) predicted creatinine clearance method (Cockcroft-Gault, CG); (3) single- or two-plasma clearance method (plasma sample clearance method, PSC). The PSC was chosen as a reference. ***Results:*** The regression equation of the Gates and the CG against the PSC was $Y = 11.89 + 1.041X$ ($r = 0.790$, $p < 0.001$, RMSE = 23.55 ml/min/1.73 m^2) and $Y = 8.845 + 0.7899X$ ($r = 0.8270$, $p < 0.001$, RMSE = 16.27 ml//min/1.73 m^2), respectively. In comparison with the GFR by PSC, the Gates tended to overestimate the GFR, and contrarily the CG tended to underestimate the GFR. ***Conclusion:*** The Gates correlates well with the PSC. However, the Gates is even less precise than the CG. The Gates' method in Tc-99m-DTPA renography is not suitable for the estimation of GFR in routine practice.

Key words: glomerular filtration rate, renography, Cockcroft-Gault's equation, plasma sample method, Tc-99m-DTPA

INTRODUCTION

INULIN CLEARANCE is proved as the gold standard for glomerular filtration rate (GFR) determination. However, this method is not performed in clinical practice, because of technical complexity and limited availability. The intrinsic creatinine clearance has been widely performed as only alternative to inulin clearance in routine practice. This method, however, is not accurate compared to inulin clearance.[1–3] Therefore, simple and accurate determination of the GFR is still a challenge clinically.[4]

In Tc-99m-DTPA renography, the glomerular filtration rate (GFR) is calculated without blood or urine sampling.[5] Several techniques have been applied in clinical practice, because of technical simplicity and requirement for less time for the patients. The method (Gate) introduced by Gates[6] has been most common in the routine setting. Although the diagnostic accuracy of the gamma camera methods is debated,[7–15] the program is provided as a software package by manufacturers in commercially available computer systems dedicated for nuclear medicine.

The GFR can also be calculated from serum creatinine using the Cockcroft-Gault equation[16] (CG). In Gates and CG, 24-hour creatinine clearance was chosen as a reference. The equations for predicting the GFR are based on the linear relationship of the renal uptake of Tc-99m-DTPA in the Gates and serum creatinine in the CG.

A plasma sample clearance method following a single injection of radioactive marker has been proved accurate for quantification of renal function.[17–20] The method, however, is not routinely performed, because of the

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laborious and cumbersome procedures involved in dilution of an injected radioactive marker and them used for technical expertise. The author has developed a double-well single-plastic scintillation counter (DWC) which streamlines the cumbersome dilution procedure in a plasma sample method with Tc-99m-DTPA.[21] It has a potential for a simultaneous assessment of GFR in Tc-99m-DTPA renography. The GFR determined by the Gates and the CG was compared with the GFR determined by one- or two-sample plasma clearance method (PSC) using the DWC.

MATERIALS AND METHODS

Subjects

There were 133 subjects (69 males and 64 females) ranging in age from 24 to 84 years included in the study. The subjects were referred for evaluation of renal function and pathophysiology in a routine practice. They were given a wide variety of clinical diagnoses including chronic renal failure in 17 patients, diabetic nephropathy in 16, essential hypertension in 12, suspected renovascular hypertension in 6, hydronephrosis in 2, polycystic kidney in 2, renal tumor in 5, glomerulonephritis in 3, nephrosis in 2, pyelonephritis in 2, reduced renal function of an unknown cause in 7, pre-surgical renal function evaluation in 51 and others in 8. Informed consent was given before the test.

Renography

Tc-99m-DTPA was prepared in our hospital using a commercially available freeze-dried kit (Daiichi Radioisotope Laboratories, Ltd., Tokyo, Japan). The dose of 200 MBq was administered to 77 patients in whom a complete scintigraphy such as blood perfusion, sequential images and computer-assisted renogram was requested. Forty to a hundred MBq was injected to 56 patients in whom a renogram and renal function (global and split) alone were requested. Prior to the administration, the pre-injection syringe with a 3-way cock and straight needle was counted by two different devices: 1) a double-well single-plastic scintillation counter (DCM-200, Aloka Co., Tokyo, Japan) and 2) a gamma camera (E.CAM, Toshiba, Tokyo, Japan), which was attached to a low-energy general-purpose parallel-hole collimator.

The patient was hydrated with 300 m*l* of water 20 min prior to the examination. The patient lay down on a bed in the supine position. Tc-99m-DTPA was given through an indwelling butterfly needle in an antecubital vein and was followed by infusion of 20 m*l* of normal saline. Frames of 128 × 128 matrix were recorded with an online-computer, initially at one second for one minute and then at 10 seconds for 20 minutes. The post-injection syringe with a straight needle which was detached before the injection was again counted by the two devices in the same way as pre-injection.

Region of interest (ROI) over each kidney was assigned manually on the frame added from 1 to 3 minutes following injection. The semilunar background ROI around each kidney was defined, and was modified for the inferior ROIs in the original Gates.[6] The background corrected time-activity curve was generated, and the renal uptake of individual kidney for one minute from 2 to 3 minutes after the injection was calculated. The GFR (GFRgates) was automatically estimated by a commercially available computer (GMS-5500A/P, Toshiba, Tokyo, Japan) according to the Gates' algorithm. Three nuclear medicine technicians were involved in the operation of data analysis.

Predicted Creatinine Clearance (Cockcroft-Gault's method)

The GFR (GFRcg) was also predicted from the serum creatinine (SCr) level at renography using Cockcroft-Gault's equation[16]:

For men

$$\text{GFR (ml/min)} = [(140 - \text{age}) \times \text{weight}]/(\text{SCr} \times 72)$$

For women

$$\text{GFR (ml/min)} = 0.85 \times [(140 - \text{age}) \times \text{weight})/(\text{SCr} \times 72)]$$

weight: body weight (kg)

SCr: serum creatinine level (mg/d*l*)

The serum creatinine was measured by an auto-analyzer (Olympus AU-602, Tokyo, Japan) with an enzyme method. The measured SCr (normal ≤ 1.0 mg/d*l*) in the subjects ranged from 0.36 mg/d*l* to 10.0 mg/d*l* with median 0.8 mg/d*l*.

Plasma Clearance Method

Radioactivity in the post-injected syringe and plasma (m*l*) was counted by DWC. Total injected dose and plasma concentration were calculated directly without a dilution procedure of a standard injected solution.[21] The GFR (GFRp) was determined from a single-plasma concentration at 180 minute-post-injection using Christensen-Groth's equation.[22,23] The accuracy of this method is limited when the level of GFR is less than 30 m*l*/min.[20] Therefore, when the GFR was expected to be below 30 m*l*/min based on a SCr above 2.0 mg/d*l*,[24] it was determined from two plasma concentrations at 120 and 240 minute-post-injection using a slope-intercept method.[20] The measured value was finally corrected by the Brochner-Mortensen's equation for overestimation.[25] This measurement was carried out in 17 patients.

Normalization of GFR

The GFR (m*l*/min) obtained by the 3 methods was normalized for a body surface area of 1.73 m^2 according to Haycock's equation.[26]

Statistical Analysis

For method comparison, standard linear least-squares regression analysis was used. p-values of 0.05 or less in

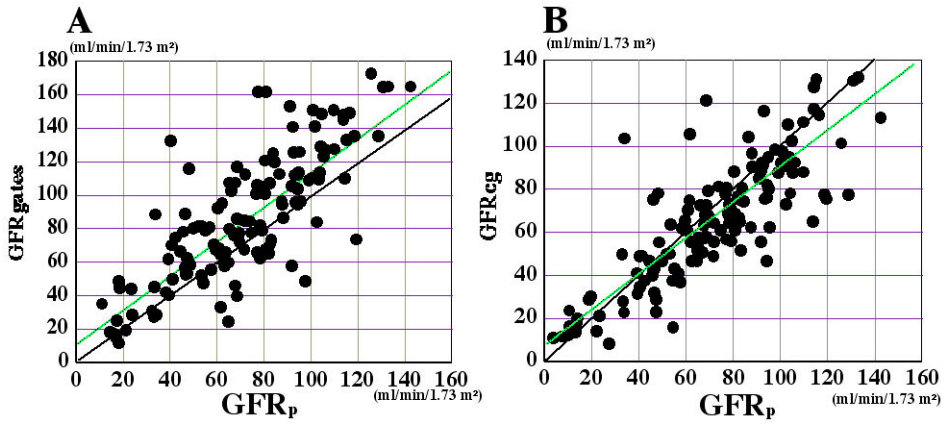

Fig. 1 Scatter plots of GFRs determined by the modified Gates' method (A) and by the Cockcroft-Gault's method (B) against that by the plasma sample method. The solid line indicates the identity line and the dotted line the regression line.

Table 1 Results on agreement of difference in GFR between the modified Gates' method or Cockcroft-Gault's method against the plasma sample method

	Difference in GFRp – GFRgates or GFRcg		
	mean	sd	95% confidence interval
Gates' method	−14.8	23.5	−10.7 ~ −18.9
Cockcroft-Gault's method	6.0	17.4	3.02 ~ 8.98

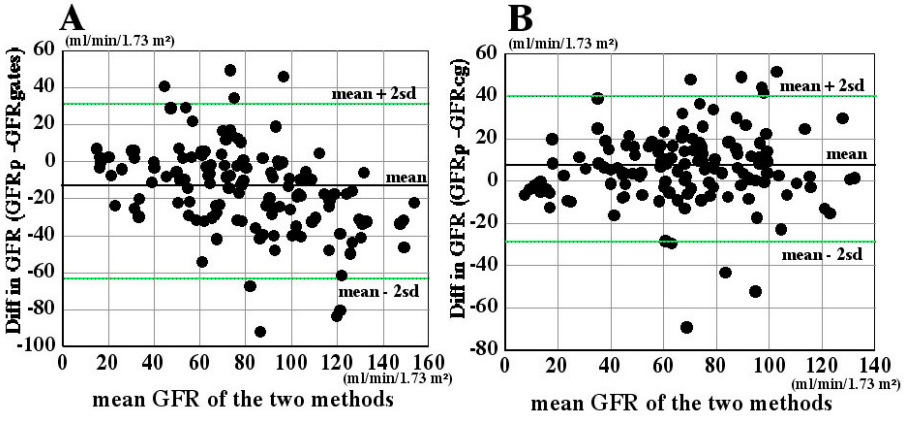

Fig. 2 Scatter plots of difference in GFRs by the modified Gates' method (A) and by the Cockcroft-Gault's method (B) against the mean GFR of the two methods. The solid line indicates the mean difference and the dotted line the 95% of agreement (2sd).

the linear regression analysis were considered significant. Bland and Altman's analysis[27] was referred to agreement between the two methods. For these analyses, a commercially available statistical software (JMP. ver. 4.0, SAS Institute Inc., Cary, NC, USA) was used.

RESULTS

The regression equation of the Gates and the CG against the PSC was $11.89 + 1.041X$ ($r = 0.790$, RMSE = 23.55 ml/min/1.73 m^2, $p < 0.001$) and $8.845 + 0.7899X$ ($r = 0.8270$, RMSE = 16.27 ml/min/1.73 m^2, $p < 0.001$), respectively (Fig. 1). Both methods correlated well with the PSC. The difference between two correlation coefficients was not statistically significant ($p = 0.390$).

Difference in the GFR (GFRp – GFRgates) and (GFRp – GFRcg) was −14.8 ± 23.5 ml/min/1.73 m^2 (mean ± sd) and 6.0 ± 17.4 ml/min/1.73 m^2, respectively (Table 1). The Gates tended to overestimate GFR, especially in the range of high GFR (Fig. 2). Mean difference between the

methods was considered to significantly deviate from zero. In contrast, the CG tended to underestimate GFR. Mean difference between the methods was small. The bias between the methods was considered not significant.

DISCUSSION

The Gates correlated well with the plasma sample method. The significant correlation of the renal uptake of Tc-99m-DTPA against the 24-hour creatinine clearance[6] has promoted this method for clinical application in routine practice. However, the Gates was proved to be inaccurate and less precise than the CG for predicting the GFR. In addition, the Gates tended to overestimate the GFR. These results were consistent with previous reports.[13,14]

It has been debated whether the Gates' method is accurate for predicting the GFR.[7–15] Several sources of errors in the estimation of GFR by scintigraphy are recognized: background correction, decay statistics, attenuation correction, estimation of arterial plasma activity, system dead time, volume measurements and radiopharmaceutical quality.[28] Of these, the bias for overestimation by the Gates may be attributable to insufficient correction of background count in the kidney. Petersen et al.[29] reports that Tc-99m-renography is more accurate than 24-hour creatinine clearance and is acceptable for clinical use in patients with reduced renal function. The limits of agreement in GFR between Tc-99m-DTPA and Cr-51 EDTA plasma clearance method ware 2 ± 17 m*l*/min. The results are different from those of the present and other studies.[7–15] The algorithm employed by them is based on that of Rehling et al.[30] and is more sophisticated than the Gates' original for the correction of the arterial background activity in the kidney. This suggests that the Gates with a simple background activity correction is less accurate than the methods with more sophisticated background activity correction for the calculation of GFR.[7,9,10] Semilunar background ROI is much better than inferior ROI for the correction of background radioactivity.[5]

Even if Tc-99m-DTPA renography is not precise as a measurement of global renal function, it provides notable information such as quantitative individual renal function and pathophysiological changes of the kidney in renovascular hypertension, hydronephrosis and renal transplant. It is suggested, that "isotopic renography is likely to be overtaken by competing technologies which can provide one test to give simultaneous information about both structure and function."[31] The GFR is quantified by the radiocontrast agent.[32] The employed algorithms have been developed in the plasma sample method with radionuclides. It is well known that renal radioactive tracers are not nephrotoxic at all. Although the employment of a sophisticated algorithm for the background correction may be expected to provide precise determination of GFR, the best way to determine GFR in Tc-99m-DTPA renography is a simultaneous employment of the PSC which only needs a few plasma samplings.[20] In these contexts, Tc-99m-DTPA renography should be performed together with a simultaneous assessment of GFR by a plasma sample method.

The plasma clearance of Tc-99m-DTPA is reported to overestimate GFR by 3.5 m*l*/min in average as compared to the renal clearance of inulin as a golden GFR marker.[33] The plasma clearance method with Tc-99m-DTPA is not considered as the gold standard for GFR determination. Nonetheless, the method has been proved as a simple and accurate alternative to the cumbersome infusion clearance method of inulin.[2,20] Finally, I would like to convey that (1) plasma sample techniques are superior to the gamma camera uptake and Cockcroft-Gault measurements of GFR; (2) the DWC makes the plasma sample measurements much easer (less laborious, less requirement for technical expertise, less time intensive); (3) the ease of plasma sample measurements provided by the DWC has the potential to allow plasma sample clearance to be simply performed as an adjunct to Tc-99m-DTPA renography and thereby provide the referring physician with an accurate measurement of GFR simultaneously with a Tc-99m-DTPA renogram.

CONCLUSION

Tc-99m-DTPA renography (Gates) is not accurate in the measurement of GFR. Gates' method is even less precise than Cockcroft-Gault's formula. Although the sophisticated algorithm for obtaining correct fractional renal uptake may improve the precision of GFR determination in Tc-99m-DTPA renography, the Gates is considered not suitable for the accurate determination of GFR.

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REFERENCES

1. Shemesh O, Golbetz H, Kriss JP, Myers BP. Limitations of creatinine as a filtration marker in glomerulopathic patients. *Kidney Int* 1985: 28: 830–838.
2. Perrone RD, Madias NE, Levey AS. Serum creatinine as an index of renal function: new insights into old concepts. *Clin Chem* 1992; 38: 1933–1953.
3. Rahn KH, Heidenreich S, Bruckner D. How to assess glomerular function and damage in humans. *J Hypertension* 1999; 17: 308–317.
4. Swan SK. The search continues—an ideal marker of GFR [editorial]. *Clin Chem* 1997; 43: 913–914.

5. Prigent A, Cosgriff P, Gates GF, Granerus G, Fine EJ, Itoh K, et al. Consensus report on quality control of quantitative measurements of renal function obtained from the renogram: International consensus committee from the Scientific Committee of Radionuclides in Nephrourology. *Semin Nucl Med* 1999; 29: 146–159.
6. Gates GF. Glomerular filtration rate: Estimation from fractional renal accumulation of ^{99m}Tc-DTPA (stannous). *AJR* 1982; 138: 565–570.
7. Russell CD, Bischoff PG, Kontzen F, Rowell KL, Yester MV, Lloyd LK, et al. Measurement of glomerular filtration rate using ^{99m}Tc-DTPA and the gamma camera: a comparison of methods. *EurJ Nucl Med* 1985; 10: 519–521.
8. Fawdry RM, Grueneward SM, Collins LT, Roberts AJ. Comparative assessment of techniques for estimation of glomerular filtration rate with Tc-99m-DTPA. *Eur J Nucl Med* 1985; 11: 7–12.
9. Russell CD, Dubovsky EV. Gates method for GFR measurement [letters to the editor]. *J Nucl Med* 1986; 27: 1373–1374.
10. Russell CD. Estimation of glomerular filtration rate using ^{99m}Tc-DTPA and the gamma camera. *Eur J Nucl Med* 1987; 12: 548–552.
11. Mulligan JS, Blue PW, Hasbargen JA. Methods for measuring GFR with technetium-99m-DTPA: an analysis of several common methods. *J Nucl Med* 1990; 31: 1211–1219.
12. Goates JJ, Morton KA, Whooten WW, Greenberg HE, Datz FL, Handy JE, et al. Comparison of methods for calculating glomerular filtration rate: technetium-99m-DTPA scintigraphic analysis, protein-free and whole-plasma clearance of technetium-99m-DTPA and iodine-125-iothalamate clearance. *J Nucl Med* 1990; 31: 424–429.
13. Duran E, Prigent A, Gaillard J. Comparison between 9 methods for estimation of glomerular filtration rate (GFR) with simultaneous injection of ^{51}Cr-EDTA and ^{99m}Tc-DTPA. In: Taylor A Jr, Nally J, Thomsen H (eds), *Radionuclides in Nephrourology*, Reston, VA; Society of Nuclear Medicine, 1997: 112–120.
14. De Santo NG, Anastasio P, Cirillo M, Santoro D, Spitali L, Mansi L, et al. Measurement of glomerular filtration rate by the ^{99m}Tc-DTPA renogram is less precise than measured and predicted creatinine clearance. *Nephron* 1999; 81: 136–140.
15. Itoh K, Tsushima S, Tsukamoto E, Tamaki N. Reappraisal of single-sample and gamma camera methods for determination of the glomerular filtration rate with ^{99m}Tc-DTPA. *Ann Nucl Med* 2000; 14: 143–150.
16. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16: 31–41.
17. Brochner-Mortensen J. Routine methods and their reliability for assessment of glomerular filtration rate in adults with special reference to total [^{51}Cr]EDTA plasma clearance. *Dan Med Bull* 1978; 25: 181–202.
18. Brochner-Mortensen J. Current status on assessment and measurement of glomerular filtration rate. *Clin Physiol* 1983; 8: 1–17.
19. Levey AS. Use of measurements of GFR to assess the progression of renal disease. *Semin Nephrol* 1989; 9: 370–378.
20. Blaufox MD, Aurell M, Bubeck B, Fommei E, Piepsz A, Russell C, et al. Report of the Radionuclides in Nephrourology Committee on renal clearance. *J Nucl Med* 1996; 37: 1883–1890.
21. Itoh K. Determination of glomerular filtration rate by means of newly developed plastic scintillation counter both with and without dilution procedures. *J Nucl Med* 2001; 42: 1484–1488.
22. Christensen AB, Groth S. Determination of ^{99m}Tc-DTPA clearance by single plasma sample method. *Clin Physiol* 1992; 19: 827.
23. Watson WS. A simple method of estimating glomerular filtration rate [letters to the editor]. *Eur J Nucl Med* 1992; 19: 827.
24. Itoh K, Tsushima S, Tsukamoto E, Tamaki N. Accuracy of plasma sample method for determination of glomerular filtration rate with ^{99m}Tc-DTPA. *Ann Nucl Med* 2002; 16: 39–44.
25. Brochner-Mortensen J. A simple method for the determination of glomerular filtration rate. *Scand J Clin Lab Invest* 1972; 30: 271–274.
26. Haycock GB, Schwartz GJ, Wisotsky DH. Geometric method for measuring body surface area: a height-weight formula validated in infants, children and adults. *J Pediatrics* 1978; 93: 62–66.
27. Bland JM, Altman D. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; ii: 307–310.
28. Russell CD. In: Tauxe WN, Dubovsky EV (eds), *Nuclear Medicine in Clinical Urology and Nephrology*, Norwalk, CT; Appleton-Century-Crofts, 1985: 173–184.
29. Petersen LJ, Petersen JR, Talleruphuus U, Moller TA, Ladefoged SD, Mehlsen J, et al. Glomerular filtration rate estimated from the uptake phase of ^{99m}Tc-DTPA renography in chronic renal failure. *Nephrol Dial Transplant* 1999; 14: 1673–1678.
30. Rehling M, Moller ML, Lund JO, Jensen KB, Thamdrup B, Trap-Jensen J. ^{99m}Tc-DTPA gamma-camera renography: normal values and rapid determination of single-kidney glomerular filtration rate. *Eur J Nucl Med* 1985; 11: 1–6.
31. Woolfson RG, Neild GH. Renal nuclear medicine: can it survive the millennium? *Nephrol Dial Transplant* 1998; 13: 12–14.
32. Lewis R, Kerr N, Van Buren C, Lowry P, Sandler C, Fraser OH, et al. Comparative evaluation of urographic contrast media, inulin, and ^{99m}Tc-DTPA clearance methods for determination of glomerular filtration rate in clinical transplantation. *Transplantation* 1989; 48: 790–796.
33. Rehling M, Moller ML, Thamdrup B, Lund JO. Trap-Jensen J. Simultaneous measurement of renal clearance and plasma clearance of ^{99m}Tc-labelled diethylenetriaminepentaacetate, ^{51}Cr-labelled ethylen-diaminetetra-acetate and inulin in man. *Clin Sci* 1984; 66: 613–619.