

Estimation of glomerular filtration rates with Technetium-99m DTPA: Comparison of uptake index method with integration method.

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Problem/background : *The evaluation of the glomerular filtration rate (GFR) with Tc-99m DTPA using single injections with multiple blood samples (plasma clearance) is a standard and reliable method but the procedure is complicated and not suitable for routine clinical use. Alternatively, GFR can be determined by a Tc-99m DTPA gamma camera method with several advantages such as simplicity blood or urine samples not needed, ability to determine separate renal functions, etc. Several gamma camera methods have been reported for this purpose. There are advantages and disadvantages among each of these methods.*

Objective : *Compare the accuracy of two methods in estimation of GFR i.e. the uptake index and integration methods by comparing the results with GFR determined by the gold standard single injection with multiple blood samples method.*

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- Setting** : *Division of Nuclear Medicine, Department of Radiology, Chulalongkorn Hospital, Thai Red Cross Society, Bangkok 10330, Thailand.*
- Research design** : *Retrospective*
- Patients** : *There were 47 subjects, 7 normal volunteers and 40 patients with glomerulonephritis disease.*
- Methods** : *The renal functions using Tc-99m DTPA is measured by the single injection with multiple blood samples method and acquired images with the gamma camera simultaneously. GFR is calculated by the single injection with multiple blood samples method and both gamma camera methods i.e. uptake index and integration methods. The correlation of each gamma camera method with multiple blood samples method is determined.*
- Results** : *Correlation coefficients and standard errors of estimation for the uptake index method and the single injection with multiple blood samples method were 0.9121 and 10.96 ml/min respectively. Correlation coefficients and standard errors of estimation for the integration method and the single injection with multiple blood samples method were 0.7189 and 18.59 ml/min, respectively.*
- Conclusion** : *Estimation of GFR using the gamma camera with uptake index method is more accurate with better correlation coefficients and smaller standard errors of estimation than using the integral methods.*
- Key words** : *Glomerular filtration rate, Tc-99m DTPA, Uptake index method, Integration methods.*

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ปัญญา ภาสว้าง, ธวัชชัย ชัยวัฒนรัตน์, สันติ สนทราพรพล. การศึกษาเปรียบเทียบการประมาณค่าอัตราการกรองของไตด้วยเทคนิคซีเอ็ม-99 เอ็ม ดีทีพีเอ โดยวิธีอัลเทคอินเด็ค และวิธีอินทิเกรชัน. จุฬาลงกรณ์เวชสาร 2540 มิ.ย; 41(6): 439-53

- ปัญหา/เหตุผล** : เจาะเลือดหลายครั้งหลังจากฉีดสารเภสัชรังสีแล้ว ถือว่าเป็นวิธีมาตรฐานและเชื่อถือได้ดี อย่างไรก็ตามวิธีนี้มีขบวนการที่ยุ่งยากไม่เหมาะสมที่จะนำมาใช้ในทางคลินิก ทางเลือกอื่นที่สามารถทำได้คือการใช้เทคนิคซีเอ็ม-99 เอ็ม ดีทีพีเอ และถ่ายภาพด้วยแกมม่าคาเมรา จากนั้นจึงคำนวณค่าอัตราการกรองของไตจากภาพถ่าย วิธีนี้มีข้อดีคือทำได้ง่าย ไม่ต้องเจาะเลือด ไม่ต้องเก็บปัสสาวะและยังสามารถคำนวณอัตราการกรองของไตแต่ละข้างได้ด้วย มีผู้ทำการศึกษาโดยใช้แกมม่าคาเมรานี้หลายวิธีด้วยกัน แต่ละวิธีก็มีข้อดีข้อด้อยต่างๆ กัน
- วัตถุประสงค์** : เปรียบเทียบความถูกต้องของการประมาณค่าอัตราการกรองของไตด้วยเทคนิคซีเอ็ม-99 เอ็ม ดีทีพีเอ ระหว่างคำนวณโดยวิธี uptake index และวิธี integration โดยใช้วิธีเจาะเลือดหลายครั้งหลังจากฉีดสารเภสัชรังสีเป็นวิธีมาตรฐานในการหาค่าอัตราการกรองของไต
- สถานที่ที่ทำการศึกษา** : สาขาเวชศาสตร์นิวเคลียร์ ภาควิชารังสีวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
- รูปแบบการวิจัย** : การศึกษาย้อนหลัง
- ผู้ป่วยที่ทำการศึกษา** : อาสาสมัครปกติ 7 ราย และผู้ป่วย glomerulonephritis 40 ราย
- วิธีการศึกษา** : ตรวจวัดการทำงานของไต หลังจากฉีดเทคนิคซีเอ็ม-99 เอ็ม ดีทีพีเอ โดยวิธีเจาะเลือดหลายครั้ง และวิธีแกมม่าคาเมรา ทำการคำนวณอัตราการกรองของไตจากวิธีเจาะเลือดหลายครั้ง และโดยวิธีแกมม่าคาเมรา 2 วิธีจากภาพถ่ายที่ได้ คือ วิธี uptake index และวิธี integration จากนั้นหาความสัมพันธ์ระหว่างค่าที่คำนวณได้จากวิธีแกมม่าคาเมราทั้งสอง กับวิธีมาตรฐาน ด้วยสถิติถดถอยเชิงเส้น เพื่อเปรียบเทียบสัมประสิทธิ์ความสัมพันธ์และค่าความผิดพลาดมาตรฐาน

- ผลการศึกษา** : ค่าสัมประสิทธิ์ความสัมพันธ์ (r) และค่าความผิดพลาดมาตรฐาน ($Sy.x$) ระหว่างวิธีมาตรฐานกับวิธี uptake index เท่ากับ 0.9121 และ 10.96 มิลลิตร/นาที่ ตามลำดับ ค่าสัมประสิทธิ์ความสัมพันธ์ (r) และค่าความผิดพลาดมาตรฐาน ($Sy.x$) ระหว่างวิธีมาตรฐานกับวิธี integration เท่ากับ 0.7189 และ 18.59 มิลลิตร/นาที่ ตามลำดับ
- สรุป** : การประมาณค่าอัตราการกรองของไตด้วยเทคนิคซีเอ็ม-99 เอ็ม ดีทีพีเอ โดยวิธี uptake index ถูกต้องกว่าวิธี integration โดยมีสัมประสิทธิ์ความสัมพันธ์กับวิธีมาตรฐานดีกว่าและมีค่าความผิดพลาดน้อยกว่า
- คำสำคัญ** : อัตราการกรองของไต, เทคนิคซีเอ็ม-99 เอ็ม ดีทีพีเอ, uptake index method, integration method.

The most popular method for glomerular filtration rate (GFR) calculation using a gamma camera technique relates the fractional activities within each kidney region of interest (ROI) during a fixed period of time to that of total injected activities.^(1,2) This method of calculation, sometime called the "integral" method, is quite accurate, especially in patients with good renal functions. However, when renal function becomes severely impaired there will be a significant amount of Tc-99m DTPA activity left in the circulation. And because the integration method takes both the activities in the renal tubules and the activities in the renal vascular pool in the calculation, over estimation of GFR can be expected in patients with severely impaired renal function.

Another method of calculation, the "uptake index" method, the GFR is calculated by taking into consideration not only the rate of radiotracer accumulation in each kidney but also correcting for intrarenal vascular activity.^(3,4) So, theoretically, the uptake index method should result in a more accurate GFR estimation.

The aim of this study was to compare the correlation and standard error of estimation of these two methods with the gold standard multiple blood sample plasma clearance method.

Subjects

There were 47 subjects included in this study. Twenty-five were males and 22 were

females. Of these, 7 were normal volunteers and 40 were glomerulonephritic patients who were referred to the nuclear medicine division for renal function studies. The average age was 31.32 ± 11.09 years (mean \pm SD) (range 17-61 years).

Methods

Both the single injection with multiple blood samples method and the gamma camera methods were studied simultaneously in each subject. No special subject preparation was required. The entire procedure was explained to the patient. Each subject's height and weight were measured (in centimeters and kilograms) at the time of the examination.

Single injection with multiple blood samples method

1. Tc-99m DTPA 2-7 mCi was drawn into 3 ml disposable syringes.
2. Both preinjection and postinjection syringes were weighed for injected dose calculation.
3. The radiopharmaceutical was injected via an antecubital vein.
4. Five ml blood samples were drawn at 10, 20, 30, 40, 50, 65, 80, 120, 180, and 240 minutes after radiopharmaceutical injection.
5. One ml of plasma from each blood sample was separated and counted for Tc-99m DTPA activity.

6. Then the count rate was plotted on a logarithmic y axis against time on linear x axis.

7. The plasma clearance of the Tc-99m DTPA was calculated by the double exponential model using the technique described by Sapirstein LA et al.⁽⁵⁾

Gamma camera method

A GE STARCAM 400AC/T gamma camera with a parallel-hole, low-energy collimator was used.

1. One minute preinjection and postinjection images were acquired.

2. The detector was set at a center energy of 140 keV with a 20% window and 128x128 matrix size.

3. The subject was laid supine on the table.

4. The detector was placed posteriorly covering the subject's heart and kidneys.

5. Two phase dynamic images were acquired with 1 second per frame for 60 frames

and 20 seconds per frame for another 60 frames, respectively. At the end of dynamic study, static images of both lateral views were acquired for kidney depth measurements.

6. Five ROIs i.e. two kidney ROIs, two infero-lateral semilunar background ROIs for each kidney and a cardiac ROI were drawn.

7. The time-activity curves of these ROIs were then created.

Calculation of GFR by the "Integration" method⁽¹⁾

Details of this method were previously explained.⁽¹⁾ In brief, each renal time-activity curve was subtracted from the background time-activity curve of the same side and attenuation correction for kidney depth was performed. Then integration of activities under each corrected kidney time-activity curve during the 2-3 minute period was calculated. Then the GFR was calculated by the formula:

$$\text{GFR} = \frac{\text{right kidney activity} + \text{left kidney activity}}{\text{preinjection counts} - \text{postinjection counts}} * 100 * 9.75621 - 6.19843$$

where:

right kidney activity = background subtracted and depth corrected right kidney activities during 2-3 minute period

left kidney activity = background subtracted and depth corrected left kidney activities during 2-3 minute period

Calculation of GFR by the "Uptake index" method^(3,4)

The kidney time-activity curve (R(t)) consists of Tc-99m DTPA activity in the renal vascular pool (rv(t)) and renal tubules (rt(t)).

$$R(t) = rv(t) + rt(t) \dots\dots\dots (1)$$

Considering only the first three minutes, there will be no significant excretion of Tc-99m DTPA from the kidney, so the renal tubules component will be proportional to the integral of the vascular time-activity curve from time zero to time 't' (3 minutes in this case) and the renal vascular pool component at time 't' will be proportional to the vascular time-activity curve at time 't' as shown in the equation.⁽¹⁾

$$R(t) = F \cdot B(t) + K \cdot \int_0^t B(t) dt \dots\dots\dots (2)$$

where:

- B(t) = activity of vascular (in cardiac ROI) at time t
- F = ratio renal vascular activity: cardiac vascular activity
- K = 'uptake index' or ratio of activity taken up by the kidney:
cardiac vascular activity

Equation⁽¹⁾ may be re-arranged by dividing each term with B(t) to produce a straight line equation which can be solved to produce F and K as shown in equation.⁽³⁾

$$\frac{R(t)}{B(t)} = F + \frac{K \cdot \int_0^t B(t) dt}{B(t)} \dots\dots\dots (3)$$

However, since the kidney and heart depths are not the same, R(t) and B(t) have to be multiplied by depth correction factors.

$$\frac{R(t)}{B(t)} \cdot \frac{d_k}{d_h} = F + \frac{K \cdot \int_0^t B(t) dt}{B(t)} \cdot \frac{d_h}{d_h} \dots\dots\dots (4)$$

$$\frac{R(t)}{B(t)} * \frac{d_k}{d_h} = F + \frac{K * \int_0^t B(t) dt}{B(t)} \dots\dots\dots (5)$$

Where:

- d_h = cardiac depth correction factor
- d_k = kidney depth correction factor
- = $e^{\mu x}$ (μ = soft tissue attenuation coefficient of Tc-99m, x = cardiac or kidney depth)

Then the activity of the kidney ROI was subtracted by the background activity (Bg(t)) as shown in equation.⁽⁶⁾

$$\frac{R(t)-Bg(t)}{B(t)} * \frac{d_k}{d_h} = F + \frac{K * \int_0^t B(t) dt}{B(t)} \dots\dots\dots (6)$$

$$\frac{R(t)-Bg(t)}{B(t)} = F * \frac{d_h}{d_k} + \frac{K * \frac{d_h}{d_k} * \int_0^t B(t) dt}{B(t)} \dots\dots\dots (7)$$

Equation (7) is a linear equation where:

$$Y = \frac{R(t)-Bg(t)}{B(t)}$$

$$X = \frac{\int_0^t B(t) dt}{B(t)}$$

$$\text{slope} = K * \frac{d_h}{d_k}$$

$$\text{intercept} = F * \frac{d_h}{d_k}$$

On plotting this equation, only data from t=1 to t=3 minutes were used.

The uptake index K can be rewritten as: $\text{slope} = K * \frac{d_k}{d_h}$

The K is the proportion of vascular activity taken up by the kidney per time unit. At time zero when the vascular activity is B(0):

$$\text{Rate of renal uptake} = K * B(0) \quad (\text{counts/sec/sec}) \dots\dots\dots (8)$$

$$\text{At time zero plasma concentration} = \frac{\text{Injected dose}}{\text{Blood volume}} \quad (\text{counts/sec/ml}) \dots\dots\dots (9)$$

$$\text{Then GFR} = K * B(0) * \frac{\text{Blood volume}}{\text{Injected dose}} \quad (\text{ml/sec}) \dots\dots\dots (10)$$

From equation (10), substitute K with $\text{slope} = K * \frac{d_k}{d_h}$ and correct B(0) with cardiac depth:

$$\text{GFR} = \text{slope} * \frac{d_k}{d_h} * B(0) * d_h * \frac{\text{Blood volume}}{\text{Injected dose}}$$

$$\text{GFR} = \text{slope} * d_k * B(0) * \frac{\text{Blood volume}}{\text{Injected dose}} \quad \dots\dots\dots (11)$$

The blood volume of Thai people can be calculated from these equations.⁽⁶⁾

$$\log(\text{BVOL}) = 3.4733 + 1.0282 (\log(W) - 1.5915) \text{ for males}$$

$$\log(\text{BVOL}) = 3.4212 + 1.0086 (\log(W) - 1.5622) \text{ for females}$$

where:

BVOL = blood volume (litre)

W = body weight (kilogram)

Results

The detailed results of the GFR computation in each subject by the three methods of analysis are shown in Table 1. Figure 1. shows graphical correlation of the GFR calculated by the uptake index and the integral gamma camera methods with the standard method. The correlation coefficient (r) and standard error of estimation

($S_{x,y}$) between the standard method and the "uptake index" method are 0.9121 and 10.96 ml/min, respectively. While the correlation coefficient (r) and standard error of estimation ($S_{x,y}$) between the standard method and the "integration" method are 0.7189 and 18.59 ml/min, respectively.

Table 1. Details of glomerular filtration rate results calculated by three methods in each individual subject.

Case No.	Glomerular filtration rate (ml/min)		
	Standard method	Uptake index method method	Integration
1	14.03	7.78	41.64
2	69.17	89.66	108.56
3	64.88	88.21	129.53
4	54.38	41.95	71.32
5	55.39	60.57	84.45
6	40.01	33.13	51.45
7	79.38	121.26	120.03
8	110.29	119.27	160.49
9	67.49	83.21	110.48
10	90.00	95.88	118.60
11	95.00	110.77	103.87
12	112.12	112.81	63.66
13	86.98	86.59	79.06
14	90.77	97.50	90.44
15	80.46	86.03	120.69
16	82.00	91.09	105.71
17	94.09	90.01	112.40
18	44.31	39.83	58.90
19	65.35	77.29	86.56

Table 1. Continue

Case No.	Glomerular filtration rate (ml/min)		
	Standard method	Uptake index method method	Integration
20	34.92	36.40	53.59
21	67.41	85.96	121.93
22	0.87	0.00	5.58
23	102.42	131.42	176.47
24	99.83	85.69	94.35
25	73.42	79.53	83.42
26	54.68	49.82	83.52
27	49.31	34.95	87.96
28	71.02	93.27	93.02
29	88.29	80.89	82.15
30	67.00	59.97	78.64
31	69.49	77.29	67.23
32	84.99	95.99	134.26
33	43.00	56.87	95.01
34	79.95	72.63	86.05
35	79.37	92.10	122.70
36	104.80	99.74	111.38
37	32.70	47.36	45.47
38	100.65	111.65	179.85
39	83.56	90.75	114.16
40	9.26	5.48	30.96
41	90.04	109.28	101.77
42	62.32	97.26	64.21
43	49.44	61.13	94.23
44	102.39	144.72	102.07
45	32.04	48.68	77.77
46	73.04	89.13	88.26
47	67.49	77.88	79.09

Estimation of glomerular filtration rate with Technetium-99m DTPA: Comparison of two gamma camera methods.

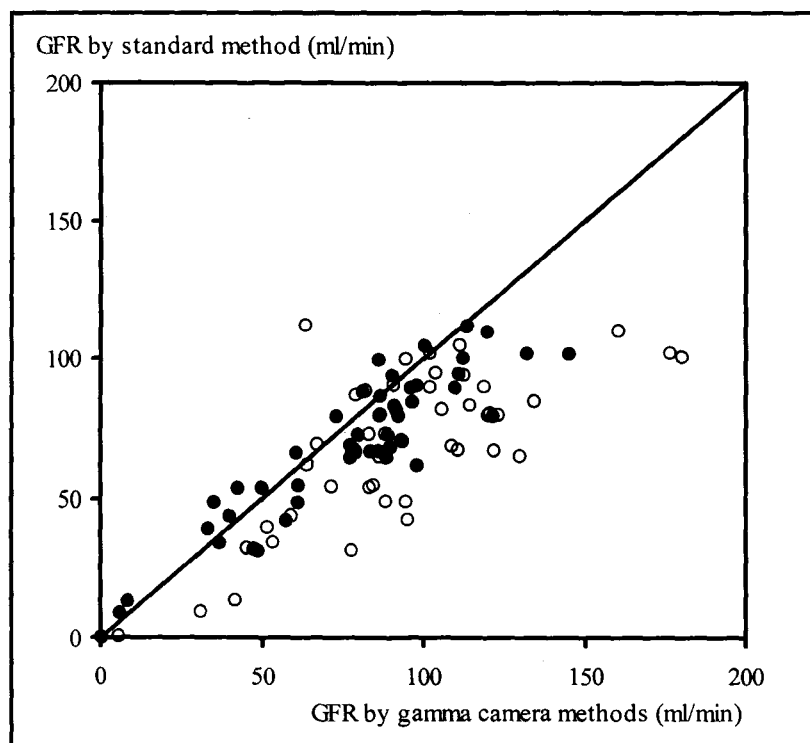


Figure 1. Graphical correlation of GFR calculated by integral (open circle) and uptake index (close circle) gamma camera methods on x axis with standard method on y axis. The straight line is line of identity.

Discussion

Several gamma camera techniques have been proposed to make calculation of GFR easy and accurate enough for routine use. Among these are the single^(7,8) or double^(9,10) blood samples, integration^(1,2) and uptake index^(3,4) methods. The integration method is perhaps the most popular method due to its simplicity. The accuracy of this method is widely accepted to be good enough for routine clinical evaluation of renal functions. However, in our experience such an accuracy can be expected only when the renal function is fairly good. When renal impairment becomes severe there will be a considerable Tc-99m DTPA left in the vascular compartment including the renal vascular space. This activity

will contribute a significant count to the renal time-activity curve. If no attempt is made to correct for such a vascular activity, over estimation of the renal function will occur. Even if background subtraction of the renal time-activity curve is applied, this still cannot be corrected for the renal vascular activity. Background activity used for subtraction is mostly the extravascular activity which can be corrected only activity from tissue overlying and underlying the kidney and extravascular activity in the kidney itself. This effect is well shown in our study. Figure 1 shows that most data calculated by the integration method (open circle) are below the line of identity which means that they over estimate the reference values.

On the contrary, the uptake index method takes into consideration the renal vascular activity which contributes a significant amount to the height of the renal time-activity curve as shown in equation⁽¹⁾. Though renal vascular activity cannot be directly measured, it is proportional to the cardiac vascular activity where we use it for estimation of renal vascular activity.^(3,4) As shown in figure 1, GFRs estimated by the uptake index method have better correlation coefficients than the standard method, and with smaller standard errors of estimation. And there is a very small bias of the method as evidence that the GFR values scatter quite well around the line of identity.

To this point, the uptake index method seems to be a promising method. However, there are two potentially correctable sources of error i.e. kidney depth values and blood volume calculation. Some studies used equations to calculate kidney depths.^(1,4) Obviously kidney depths calculated by equation are unreliable⁽¹¹⁾ and cannot be applied to patients in different countries and from different races. Also, the right and left kidneys are not at the same depth from the body surface. Other studies used ultrasonograms to calculate kidney depths.^(12,13) However this is very inconvenient especially in those departments where an ultrasonogram machine is not available. Therefore, we used lateral images at the end of the study for this purpose. Although using lateral images is convenient and always available, in some cases it creates much error, especially in patients whose

renal functions are very good because there is only a small amount of activity remaining at the end of the studies. We suggest one alternative way to solve this problem (but we have not done it ourselves because we do not have a dual headed gamma camera). If images are acquired using a dual headed gamma camera at each period of time, we then have two images i.e. anterior and posterior views and 3 equations can be created.

$$\text{Count}_A = \text{Count}_T * e^{-\mu y}$$

$$\text{Count}_P = \text{Count}_T * e^{-\mu x}$$

$$\text{Body thickness} = x + y$$

where: Count_A = Renal counts measured from anterior view

Count_P = Renal counts measured from posterior view

Count_T = True renal counts

μ = Soft tissue attenuation coefficient of Tc-99m

y = kidney depth measure from anterior body surface to center of kidney

x = kidney depth measure from posterior body surface to center of kidney

From the 3 equations above, we have 3 unknowns, i.e. ' Count_T ', ' x ' and ' y ', so we can solve these equations to get ' x ' for kidney depth correction or even get true renal activities for calculation without depth correction being needed when dual headed gamma camera is used.

For the second source of error, blood volume, one set of blood volume equations cannot be applied to patients from different countries and from different races. Also, some patients may present with abnormal blood volumes which cannot be correctly calculated by equation. An alternative way is to report GFR as a relative value, i.e. 'uptake index', rather than absolute value. Based on the fact that the kidneys receive about 20% of total cardiac blood output, hence 20% of total blood volume. And assuming that normal hematocrit is 0.45, then the kidneys receive plasma or renal plasma flow about 11% of blood volume. Twenty percent of renal plasma flow is GFR.⁽¹⁴⁾ Then the GFR will be 2.2% of the blood volume. This value is actually a "normal uptake index" and it is independent of blood volume. If the calculated uptake index is 1.1%, the clinician will know that this patient has lost 50% of his renal function. This may be a logical method of GFR expression because it is independent of blood volume. For example, one patient with a blood volume of 4000 ml may have a GFR of 88 ml/min. Another patient with a blood volume of 5000 ml may have a GFR of 110 ml/min. Both have normal GFRs with equal uptake indexes of 2.2% even though they have 22 ml/min differences in GFR.

Conclusion

We conclude that GFR calculation using a gamma camera and the "uptake index" method is easy to perform and provides a more accurate

GFR value compared to the "integration" method. The possible sources of error are kidney depth measurement and blood volume estimation. These problems potentially can be solved using a dual headed gamma camera and by presenting the GFR value as a relative percentage value to blood volume rather than presenting it as an absolute value.

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