Correlation of the ERPF with the Extraction Fraction Values of Technetium-99m Mercaptoacetyltriglycine

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Objective: *The objective of this study was to determine if a correlation exists between the effective renal plasma flow (ERPF) and the extraction fraction (EF) using ^{99m}Tc MAG3 in children. This EF has been previously described with ^{99m}Tc DTPA. However, the renal imaging agent of choice has become ^{99m}Tc MAG3.*
Material and Method: *The study was approved by The Children's Hospital of Philadelphia's institutional review board. Informed consent was also obtained. A retrospective study of 29 children (16 males, 13 females) of ages 1 month to 19.5 years who underwent 99mTc MAG3 renal scintigraphy from September 2001 to December 2001 was analysed. EF values were calculated with and without attenuation correction in each kidney by determining the counts in a region of interest, correcting for background and comparing the counts with the injected dose. The EF was compared to the ERPF calculated using the Schlegel's method. The correlation between the EF and the ERPF, corrected and non-corrected for soft tissue attenuation, were determined and were identified by using linear regression analysis.*
Results: *There was significant correlation between the ERPF and the EF with ($r = 0.62$, $p < 0.05$ on the left, $r = 0.51$, $p = 0.005$ on the right) than without attenuation correction ($r = 0.54$, $p = 0.003$ on the left, $r = 0.42$, $p = 0.022$ on the right).*
Conclusion: *These results indicate a correlation of the ERPF calculated using the Schlegel's method with EF obtained from a ^{99m}Tc MAG3 renal scintigraphy. The EF may be the good alternative parameter for calculation of renal function, potentially more practical in pediatric patient and the ERPF for ^{99m}Tc MAG3 using the established software program based on Schlegel's formula.*

Keywords: *Extraction fraction, Mercaptoacetyltriglycine, Estimated renal plasma flow, Renography, MAG3*

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Technetium-99m Mercaptoacetyltriglycine (MAG3) was introduced as a replacement for Iodine-131 Orthoiodohippurate (OIH) for renography studies and measurement of renal function, especially in infants and children due to the favourable dosimetry and excellent imaging qualities of the compound[1-5]. For quantification of renal function using radionuclides, several techniques have been reported as references[6,7].

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Gamma camera based methods are a potentially advantageous alternative because they do not require blood sampling. Effective renal plasma flow (ERPF) is also used to monitor renal function. The ERPF can be calculated with a gamma-camera based method by using Schlegel's formula[8], which is often implemented in commercially available software packages. However, the limitation of this method is that it was originally demonstrated for OIH clearance, which is not suitable in clinical practice for infants and children.

The EF has previously been described as a good indicator for individuals as well as for global kidney function[9]. The authors routinely determine an EF with MAG3 as a parameter of renal function for each kidney, expressed from the activity accumulated during minute 1 to 2 after injection as a percentage of the injection dose. To date, no study has reported the correlation between the ERPF based on Schlegel's formula and the EF for MAG3 in a camera based technique.

To assess the correlation between ^{99m}Tc MAG3 ERPF and EF by the gamma camera based method in children, the authors compared the ERPF calculated with Schlegel's method and the EF calculated as a percentage of the injected dose and to determine if the ^{99m}Tc- MAG3 ERPF could be used directly as a measure of renal function in clinical practice.

Material and Method

The study was approved by The Children's Hospital of Philadelphia's institutional review board and informed consent was obtained. There is no financial conflict of interest. This study was performed during one of the authors' (Chanisa Chotipanich) study, supported by International Atomic Energy Agency (IAEA) fellowship at Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania.

Patient population

A retrospective study of the patients who performed 99mTc MAG3 renal scintigraphy from September 2001 to December 2001 was analysed. Fifty-eight renal units in 29 patients (16 boys, 13 girls), age 1 month to 19.5 years (mean age, 2.20 years; median age, 0.45 years), were studied after having received informed consent. Patient data are shown in Table 1.

Dose injection

The syringe with the radioactive dose of ^{99m}Tc MAG3 was counted by placing it in the centre of the

Table 1. Patient data

Patient No.	Age (Yr)	Sex	%EF RT	%cEF RT	ERPF (ml/min) RT	%EF LT	%cEF LT	ERPF (ml/min) LT
1	0.21	F	0.1	0.1	4.5	5.5	7.4	302.7
2	0.24	F	4.6	6.2	99.3	3.9	5.3	233.0
3	0.05	M	2.6	3.4	123.7	0.5	0.6	25.5
4	1.84	F	4.6	6.6	159.9	4.6	6.5	168.9
5	0.24	M	5.9	7.9	159.9	6.0	8.1	160.1
6	0.13	F	6.5	8.7	163.1	1.4	1.9	7.8
7	0.20	M	8.2	11.1	167.0	8.1	10.9	146.0
8	1.22	F	2.1	3.1	173.8	2.3	3.4	165.8
9	3.59	M	5.7	7.9	177.0	2.4	4.7	116.6
10	0.33	M	6.1	8.4	177.0	6.6	9.1	241.0
11	0.20	M	5.0	6.8	197.5	5.0	6.8	199.9
12	0.41	F	3.9	5.2	204.0	3.7	4.9	190.6
13	1.83	M	7.5	11.7	212.4	6.6	10.2	286.5
14	0.26	M	6.2	8.4	214.4	7.9	10.7	241.4
15	6.29	M	7.0	4.3	251.6	4.0	7.5	397.0
16	19.46	F	1.6	4.4	259.3	3.2	8.7	244.5
17	0.45	F	4.6	6.9	263.0	4.8	7.1	249.7
18	0.43	F	6.0	8.4	274.0	7.0	9.9	292.0
19	0.37	M	6.0	8.4	287.0	6.9	9.6	324.0
20	1.40	M	5.7	8.6	288.6	6.4	9.7	381.2
21	0.07	M	1.8	3.2	301.7	1.3	2.3	291.9
22	0.66	M	4.0	7.4	325.2	4.3	6.6	299.3
23	5.06	F	5.7	8.9	328.2	6.7	10.0	359.0
24	3.98	M	3.8	5.7	361.3	3.6	5.4	325.7
25	1.45	M	2.7	3.9	371.5	2.0	3.0	321.0
26	10.41	F	4.7	7.8	383.8	4.6	7.7	318.8
27	2.20	M	6.3	9.5	392.2	3.8	5.6	231.3
28	0.24	F	8.5	11.6	462.6	0.1	0.1	5.3
29	0.86	F	10.7	15.0	532.0	0.8	1.1	29.6

% cEF= % extraction fraction with attenuation correction field of view for exactly 30 centimetres below a large FoV gamma camera (ADAC-SKYLIGHT) fitted with a low energy high resolution collimator. Ten-second image acquisition of the syringe was obtained pre and post injection.

Imaging procedures

Gamma camera renography was performed on a dual head gamma camera (ADAC-SKYLIGHT) with a low energy high-resolution collimator, and a 20% window centred over the 140 keV photo peak of ^{99m}Tc. Patients remained supine on the bed above the gamma camera and were hydrated with a saline solution at 10 to 20 drops per minute during the exam. Following the intravenous injection of 74-148 MBq of ^{99m}Tc MAG3, the image data were collected in a 128x128 matrix at 1 second per frame in the initial 1 minute and, thereafter, at 30 seconds per frame for 50 minutes.

Data analysis

EF for each kidney was determined from summation of all frames between 1 and 2 or 1 and 3 minutes included, after the injection. Renal and perirenal background regions of interest (RoIs) were drawn manually around each kidney (Fig. 1). The background corrected count in each kidney was obtained with and without attenuation correction.

Determination of extraction fraction (EF)

The extraction fraction was calculated for each kidney according to the protocol of Children's Hospital of Philadelphia as follows:

EF = ((1-2 min kidney counts-Background) Y / (Pre-post syringe count) 6) 100,

Fig. 1 Regions of Interest (ROIs) for each kidney with background surrounding the individual kidney

where Y is the depth correction factor calculated from the following equation:

Depth correction factor = patient's height in centimetre / Patient's weight in pounds,

and 6 is used to convert the count from 10 second to 1 minute frames

Determination of effective renal plasma flow (ERPF)

The ERPF was calculated according to the protocol (method for ERPF analysis of Schlegel) with software provided by ADAC based on the following:

ERPF = 5.029 Body Surface Area R,

where the body surface area is calculated from:

Body Surface Area = Weight (kg)$^{0.425}$ Height (cm)$^{0.725}$ 0.007184

and R is the predicted 30-minute return of the injected nuclide, defined as:

Predicted Return = Individual kidney uptake / Total uptake and calculated on each side.

The uptake is calculated as follow:

Uptake = Background-corrected counts Kidney Depth^2 100 / One-minute count

From injection image, where

Background-corrected counts = Raw Counts - (Background counts # pixels in kidney ROI / # pixel in Background ROI)

Kidney depth was estimated from the correlations:

Right Kidney Depth = (13.3 Weight (kg) / Height (cm)) + 0.7

Left Kidney Depth = (13.2 Weight (kg) / Height (cm)) + 0.7

Statistic analysis

From this database, the authors estimated the correlation between ERPF and EF for both kidneys with and without attenuation correction. Data was analysed using SPSS version 14 (SPSS, Chicago, IL). 95% confidence intervals were presented. A p-value of less than 0.05 was considered to indicate a statistical significance. Pearson correlation coefficients were correlated for comparison between the ERPF and EF with and without attenuation correction. Simple linear regression models were fitted.

Results

The results are summarized in Table 1. Regression curves are shown in Fig. 2 and 3. The ERPF of both kidneys was found to correlate with the EF with attenuation correction, with a correlation coefficient of 0.62 for the left kidney and 0.51 for the right kidney.

A

B

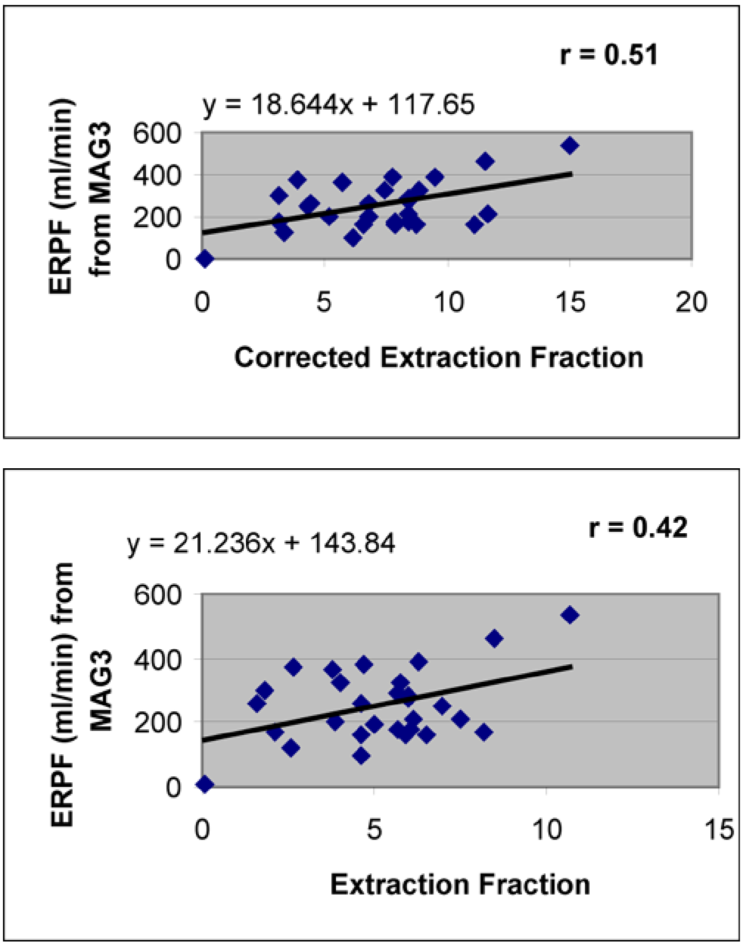


Fig. 2 Correlation between ERPF of right kidney as determined by Schlegel's formula and EF (A) with attenuation correction (B) without attenuation correction

The regression lines of left and right kidney were expressed by the equation: Y = 21.357X + 90.15, r^2 = 0.386, p < 0.05, 95%CI; 0.009, 0.027 and Y = 18.644X + 117.65, r^2 = 0.257, p = 0.005, 95%CI; 0.005, 0.023, respectively. If the EF is calculated without attenuation correction is analysed; the correlation coefficient is 0.54 for the left kidney, 0.42 for the right kidney. The equations of the left and right kidneys were Y = 26.231X + 113.95, r^2 = 0.29, p = 0.003, 95%CI; 0.004, 0.018 and Y = 21.236X + 143.84, r^2 = 0.18, p = 0.022, 95%CI; 0.001, 0.016, respectively.

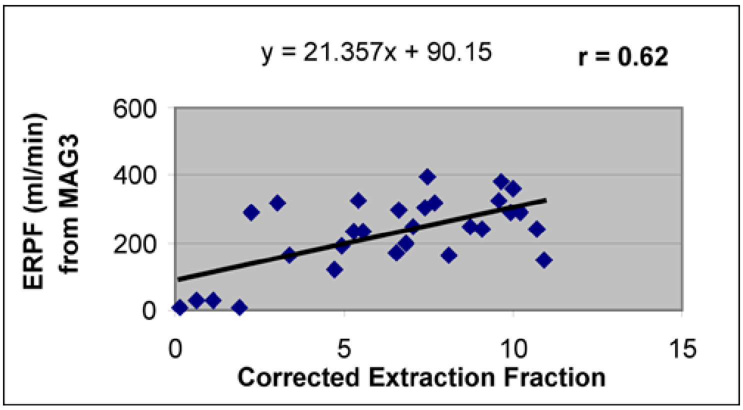
Discussion

When available, Technetium- 99m Mercaptoacetyltriglycine (MAG3) is the radiopharmaceutical agent of choice for renal scintigraphy in the evaluation of pediatric nephrourological disease[10-12]. However, there have been few studies discussing quantification of renal function with ^{99m}Tc MAG3 in children[10-18], particularly with a gamma camera based method[19-21].

The index for renal function obtained with a ^{99m}Tc MAG3 study for clearance, however, is not often familiar to clinicians and needs to be converted to effective renal plasma flow (ERPF). Higher protein binding, higher plasma concentration, lower plasma clearance and smaller volume of distribution[13-16] create high quality imaging; however, the calculation of the ERPF cannot be obtained directly from ^{99m}Tc MAG3. Therefore, a "correction factor" has been used to translate MAG3 clearance into estimated ERPF values[17]. Another drawback of ^{99m}Tc MAG3 is that software packages of gamma-camera based methods to calculate the ERPF are validated only for OIH.

Quantitative assessment of renal function is a major role of radionuclide renography and several methods have been reported to estimate MAG3 clear-

A



B

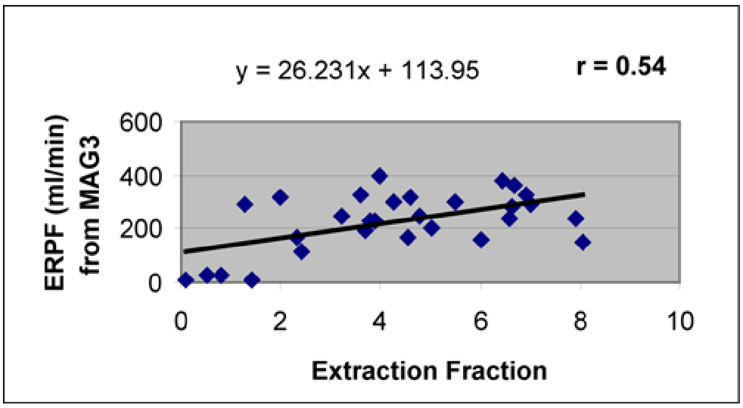


Fig. 3 Correlation between ERPF of left kidney as determined by Schlegel's formula and EF (A) with attenuation correction (B) without attenuation correction

ance[21-25] as an index of renal function. Techniques based on the gamma camera acquisition and computer post-processing, are reportedly less accurate than methods based on plasma clearance[26].

The EF is a good indicator to determine renal function. The EF correlates well with the glomerular filtration rate (GFR) as determined by the clearance from the blood of ^{99m}Tc Diethylenetriaminepentaacetic acid (DTPA) with a correlation coefficient of 0.92[9]. Kilingensmith[27] compared the renal uptake of ^{99m}Tc MAG3 at 1-2 minutes as a percent of the injected dose in 36 patients studied at least 2 days apart and reported excellent correlation (r = 0.99). Finally, Kazuo[20] reported that the renal uptake per injected dose (%RU) of the 1-min post injection correlates well with plasma clearance by a single blood sample method as the reference, using MAG3 (r = 0.910). The authors routinely measured and reported the differential renal function in terms of MAG3 EF, defined as the activity of radio-tracer present in the ROIs during the passage of the bolus 1 to 2 minutes after injection, expressed as a percentage of the injected dose. For the calculation of renal uptake from the injected dose, several factors are important, including the amount of injected dose, the definition of the region of interest (ROIs), the calculation of renal depth, the value chosen for the effective linear attenuation coefficient of 140 keV photons in the body and correction for background activity. The actual effects of these factors on the estimation of absolute renal uptake have been described by a number of authors[28-31]. Attenuation correction will lead to more accurate measurement of renal function using ^{99m}Tc MAG3.

In the present study EF values were obtained with and without attenuation correction in each kidney. The region of interest corresponds to the renal contour and is corrected for background. The injected dose was measured and compared to ERPF values based on Schlegel's method[8]. In the presented results, 58 kidneys in the 29 patients showed a better correlation between ERPF and EF with attenuation correction (r = 0.62 on the left, r = 0.51 on the right) than without it (r = 0.54 on the left, r = 0.42 on the right).

Study limitation

The current study was also limited by the small number of patients included. Therefore, it might have decreased the authors' powers to detect the true difference. Further study should be undertaken with a larger sample size.

Conclusion

The authors found statistically significant correlation between ERPF measurements based on Schlegel's method and EF using MAG3. The EF can be used as an alternative parameter for the calculation of renal function and is meaningful in long-term follow up care of pediatric patients with renal involvement. Moreover, the ERPF for ^{99m}Tc MAG3, obtained from the software program based on Schlegel's formula, can be used directly as a measure of renal function.

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References

1. Stabin M, Taylor A Jr, Eshima D, Wooter W. Radiation dosimetry for technetium-99m-MAG3, technetium-99m-DTPA, and iodine-131-OIH based on human biodistribution studies. J Nucl Med 1992; 33: 33-40.
2. Al Nahhas AA, Jafri RA, Britton KE, Solanki K, Bomanji J, Mather S, et al. Clinical experience with 99mTc-MAG3, mercaptoacetyltriglycine, and a comparison with 99mTc-DTPA. Eur J Nucl Med 1988; 14: 453-62.
3. Taylor A Jr, Ziffer JA, Eshima D. Comparison of Tc-99m MAG3 and Tc-99m DTPA in renal transplant patients with impaired renal function. Clin Nucl Med 1990; 15: 371-8.
4. Taylor A Jr, Clark S, Ball T. Comparison of Tc-99m MAG3 and Tc-99m DTPA scintigraphy in neonates. Clin Nucl Med 1994; 19: 575-80.
5. Taylor A Jr, Eshima D, Christian PE, Milton W. Evaluation of Tc-99m mercaptoacetyltriglycine in patients with impaired renal function. Radiology 1987; 162: 365-70.
6. Cohen ML. Radionuclide clearance techniques. Semin Nucl Med 1974; 4: 23-38.
7. Dubovsky EV, Russell CD. Quantitation of renal function with glomerular and tubular agents. Semin Nucl Med 1982; 12: 308-29.
8. Schlegel JU, Hamway SA. Individual renal plasma flow determination in 2 minutes. J Urol 1976; 116: 282-5.
9. Heyman S, Duckett JW. The extraction factor: an estimate of single kidney function in children during routine radionuclide renography with 99mtechnetium diethylenetriaminepentaacetic acid. J Urol 1988; 140: 780-3.
10. Piepsz A, Gordon I, Hahn K, Kolinska J, Kotzerke J, Sixt R. Determination of the technetium-99m mercaptoacetyltriglycine plasma clearance in children by means of a single blood sample: a multicentre study. The Paediatric Task Group of the EANM. Eur J Nucl Med 1993; 20: 244-8.
11. Gordon I, Anderson PJ, Lythgoe MF, Orton M. Can technetium-99m-mercaptoacetyltriglycine replace technetium-99m-dimercaptosuccinic acid in the exclusion of a focal renal defect? J Nucl Med 1992; 33: 2090-3.
12. Chapman S, Mountford PJ, Boivin CM, Burrell DN. A further application of 99Tcm-MAG3 in children. Nucl Med Commun 1992; 13: 897-8.
13. Taylor A Jr, Eshima D, Fritzberg AR, Christian PE, Kasina S. Comparison of iodine-131 OIH and technetium-99m MAG3 renal imaging in volunteers. J Nucl Med 1986; 27: 795-803.
14. Bubeck B, Brandau W, Steinbacher M, Reinbold F, Dreikorn K, Eisenhut M, et al. Technetium-99m labeled renal function and imaging agents: II. Clinical evaluation of 99mTc MAG3 (99mTc mercaptoacetylglycylglycylglycine). Int J Rad Appl Instrum B 1988; 15: 109-18.
15. Jafri RA, Britton KE, Nimmon CC, Solanki K, Al Nahhas A, Bomanji J, et al. Technetium-99m MAG3, a comparison with iodine-123 and iodine-131 orthoiodohippurate, in patients with renal disorders. J Nucl Med 1988; 29: 147-58.
16. Russell CD, Thorstad B, Yester MV, Stutzman M, Baker T, Dubovsky EV. Comparison of technetium-99m MAG3 with iodine-131 hippuran by a simultaneous dual channel technique. J Nucl Med 1988; 29: 1189-93.
17. Russell CD, Li Y, Nadiye KH, Dubovsky EV. Renal clearance of technetium-99m-MAG3: normal values. J Nucl Med 1995; 36: 706-8.
18. Bubeck B, Piepenburg R, Grethe U, Ehrig B, Hahn K. A new principle to normalize plasma concentrations allowing single-sample clearance determinations in both children and adults. Eur J Nucl Med 1992; 19: 511-6.

19. Gordon I, Anderson PJ, Orton M, Evans K. Estimation of technetium-99m-MAG3 renal clearance in children: two gamma camera techniques compared with multiple plasma samples. J Nucl Med 1991; 32: 1704-8.
20. Itoh K, Nonomura K, Yamashita T, Kanegae K, Murakumo M, Koyanagi T, et al. Quantification of renal function with a count-based gamma camera method using technetium-99m-MAG3 in children. J Nucl Med 1996; 37: 71-5.
21. Oriuchi N, Onishi Y, Kitamura H, Inoue T, Tomaru Y, Higuchi T, et al. Noninvasive measurement of renal function with 99mTc-MAG3 gamma-camera renography based on the one-compartment model. Clin Nephrol 1998; 50: 289-94.
22. Russell CD, Taylor A, Eshima D. Estimation of technetium-99m-MAG3 plasma clearance in adults from one or two blood samples. J Nucl Med 1989; 30: 1955-9.
23. Muller-Suur R, Magnusson G, Bois-Svensson I, Jansson B. Estimation of technetium 99m mercaptoacetyltriglycine plasma clearance by use of one single plasma sample. Eur J Nucl Med 1991; 18: 28-31.
24. Taylor A, Halkar RK, Garcia E, Jones M, Folks R, Carrigan P. A camera based method to calculate Tc-99m MAG3 clearance [abstract no.188]. J Nucl Med 1991; 32(5 Suppl): 953.
25. Taylor A Jr, Manatunga A, Morton K, Reese L, Prato FS, Greenberg E, et al. Multicenter trial validation of a camera-based method to measure Tc-99m mercaptoacetyltriglycine, or Tc-99m MAG3, clearance. Radiology 1997; 204: 47-54.
26. Fine EJ, Axelrod M, Gorkin J, Saleemi K, Blaufox MD. Measurement of effective renal plasma flow: a comparison of methods. J Nucl Med 1987; 28: 1393-400.
27. Klingensmith WC III, Briggs DE, Smith WI. Technetium-99m-MAG3 renal studies: normal range and reproducibility of physiologic parameters as a function of age and sex. J Nucl Med 1994; 35: 1612-7.
28. Maneval DC, Magill HL, Cypess AM, Rodman JH. Measurement of skin-to-kidney distance in children: implications for quantitative renography. J Nucl Med 1990; 31: 287-91.
29. Cosgriff P, Brown H. Influence of kidney depth on the renographic estimation of relative renal function. J Nucl Med 1990; 31: 1576-7.
30. Taylor A, Lewis C, Giacometti A, Hall EC, Barefield KP. Improved formulas for the estimation of renal depth in adults. J Nucl Med 1993; 34: 1766-9.
31. Taylor A Jr, Corrigan PL, Galt J, Garcia EV, Folks R, Jones M, et al. Measuring technetium-99m-MAG3 clearance with an improved camera-based method. J Nucl Med 1995; 36: 1689-95.

***ความสัมพันธ์ระหว่างค่า** Effective renal plasma flow **และ** Extraction fraction **โดยใช้** ^{99m}Tc-MAG3*

ชนิสา โชติพานิช, มาร์ค ฮิกเกอร์สัน, เจเฮนเซฟ คาน, เดฟ เบนจามิน, ดักลัส แคนนิ่ง, มาร์ติน ชาล์รอน

***วัตถุประสงค์**: เพื่อศึกษาความสัมพันธ์ระหว่างค่า ERPF และ EF โดยใช้ ^{99m}Tc-MAG3*

***วัสดุและวิธีการ**: ทำการศึกษาย้อนหลัง ผู้ป่วยเด็กจำนวน 29 ราย ที่มารับการตรวจที่The Children's Hospital of Philadelphia ในระหว่างเดือนกันยายน พ.ศ. 2544 ถึง เดือนธันวาคม พ.ศ. 2544 โดยเป็นผู้ชาย 16 ราย ผู้หญิง 13 ราย อายุเฉลี่ย 2.2 ปี (1 เดือน ถึง 19.5 ปี) ศึกษาโดยวิธีการตรวจ Renal scintigraphy (^{99m}Tc-MAG3) โดยที่ค่า EF ที่วิเคราะห์ได้มาจากวิธีการตรวจแก้ไขและไม่ตรวจแก้ไขค่าการดูดกลืนรังสี (attenuation) ของไตในแต่ละข้าง เปรียบเทียบความสัมพันธ์ระหว่างค่า EF กับ ค่า ERPF ทางสถิติด้วยวิธี Linear regression analysis*

***ผลการศึกษา**: มีความสัมพันธ์ระหว่างค่า ERPF กับค่า EF ที่ตรวจแก้ไขค่าการดูดกลืนรังสี (attenuation) ของไตในแต่ละข้างอย่างมีนัยสำคัญทางสถิติ โดยมีค่าสัมประสิทธิ์สัมพัทธ์ (r) เท่ากับ 0.62 ของไตข้างซ้าย และ 0.51 ของไตข้างขวาตามลำดับ*

***สรุป**: การศึกษานี้แสดงให้เห็นว่าค่า ERPF ที่คำนวณโดย Schlegel's method และค่า EF ที่ใช้ ^{99m}Tc-MAG3 มีความสัมพันธ์กันอย่างมีนัยสำคัญทางสถิติ ดังนั้นค่า EF น่าจะถูกพิจารณานำมาใช้ในการหาค่าการทำงานของไตในผู้ป่วยเด็ก และในขณะเดียวกันสามารถใช้ Schlegel's method ในการหาค่า ERPF จาก ^{99m}Tc-MAG3 renal scan*