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Original

Normal ranges of renal function parameters for ^{99m}Tc-EC renal scintigraphy

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Abstract

BACKGROUND: Dynamic renal scintigraphy remains the recognized method for evaluation of kidney function and perfusion. Although there is an extensive body of knowledge about the use of technetium-99m-mercaptoacetyltriglycine (99mTc-MAG3), much less has been written about renal technetium-99m-ethylenedicysteine (^{99m}Tc-EC) scintigraphy.

The aim of this study was to determine the normal value of renal function parameters in ^{99m}Tc-EC dynamic renal scintigraphy: Tmax and T1/2. The effects of age, left or right side in the retroperitoneal space, and sex on those parameters were examined.

MATERIAL AND METHODS: The research was conducted on 123 patients (F/M: 70/53; aged 2–71; averaging 14.8 years of age) with at least one normal kidney. A total of 194 healthy kidneys were examined, including pediatric kidneys.

RESULTS: According to this study, the normal value of Tmax is 2.85 min (± 1.16) and T1/2 is 8.7 min (± 3.61). Values calculated for pediatric studies are Tmax is 2.81 (± 1.16) and T1/2 is 8.63 (± 3.71).

CONCLUSIONS: The normal value of secretory and excretory renal function parameters was calculated. Although the value is slightly lower for children, this is not statistically significant, as globally there are no differences between the kidney-location sides and sexes for any parameter.

KEY words: radionuclide imaging; dynamic renal scintigraphy; technetium-99m-ethylenedicysteine; pediatric renal scintigraphy; renal function; renal function parameters

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Introduction

Dynamic renal scintigraphy is based on physiological processes, is minimally invasive, and repeatable. It allows recognition of various renal abnormalities in an early stage [1, 2]. That is why it remains the gold standard for assessing renal function, despite some shortcomings of this method [3].

The studies examining the dynamic renal scintigraphy performed with the use of the ^{99m}Tc-ethylenedicysteine (^{99m}Tc-EC) in normal human volunteers revealed that the renal clearance of ^{99m}Tc-EC is higher than that of ^{99m}Tc-mercaptoacetyltriglycine (^{99m}Tc-MAG3) and more similar to that of 131I-orthoiodohippurate (OIH). ^{99m}Tc-EC is characterized by faster and more complete renal washout and similar good imaging properties [1, 4, 5].

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Dynamic renal scintigraphy includes quantitative estimates of renal perfusion and function. Through the renographic curve shows the change of the radioisotope concentration in renal parenchyma as a function of time [6]. According to the EANM, following the intravenous administration of ^{99m}Tc-EC, some part (17%) of it is filtered in the glomeruli while a major portion (50%) is secreted in the proximal part of the tubules by organic anion transporters [7]. 70% of the marker is extracted from the body after about 40 minutes and 95% after 1,5 hours following the injection [6]. Three phases can be distinguished in the dynamic renal scintigraphy a vascular phase, a parenchymatous phase (secretory), and an excretory phase with a decline in radioactivity. Three parameters can be obtained from the curve: Tmax, T1/2 and split function (uptake). Tmax is the time to reach the maximum amplitude of the observed activity, and it depends on the transport efficiency of the parenchyma. T1/2 denotes the time when radioactivity in the region of interest is reduced by half. The determination of ROI for both kidneys makes it possible to plot a create renographic curve describing the radioisotope concentration as a function of time (time-activity curves) [8]. The time-activity curve is determined

after the correction of extra-renal background as recommended by the EANM [9]. The normal state of the split function is considered to range from 45% to 55% of the total uptake for both healthy kidneys [9], although some sources give the range of 42–58% [10].

Up to date, the parameters of dynamic renal scintigraphy with ^{99m}Tc-EC have only been studied either on small groups of adult volunteers [10, 11] or a small pediatric group [12].

In light of the above, the aim of this study was to evaluate the normal value of renal function parameters in ^{99m}Tc-EC dynamic renal scintigraphy: Tmax and T1/2, basing on a larger group of patients with at least one kidney considered as normal. The effects of age left or right side in the retroperitoneal space and sex on those parameters were examined.

Material and methods

Patients

All data were collected in the Department of Nuclear Medicine over a period from 6.09.2012 to 13.11.2014 and then analyzed retrospectively. The study was performed on a population of patients referred for diagnostic tests for suspected kidney diseases or dysfunctions. Patients whose scintigraphy did not confirm the disease and patients diagnosed with one dysfunctional and one healthy kidney were included in the study. Due to a large number of tests, we examine not only patients with renal disease, but also a certain number of patients with at least one kidney considered normal in our dynamic renal scintigraphy study. 123 patients (F/M: 70/53; aged 2–71; averaging 14.8 years old) were selected from 259 patients with at least one kidney correct by visual assessment, based on the criteria listed in Table 1. The evaluation was based on 104 patients who were 2–18 years old (F/M: 61/43; aged 2–18; averaging 9.5 years old) and 19 patients above the age of 18 (F/M: 9/10; aged 21–71; averaging 43.8 years old), which does not confirm the suspicion of doctors issuing the referrals.

The total number of kidneys considered normal in the study was 194 (F/M: 113/81; 0ne /two normal kidneys: 52/142; left/right:104/90; aged 2–71; averaging 14.8 years old). There were 28 kidneys considered normal in the adult population (F/M kidneys: 12/16; left/right:16/12; aged 21–71; averaging 45.2 years old). There were 166 kidneys considered normal in the pediatric population (F/M: 101/65; left/right: 88/78; aged 2–18; averaging 9.7 years old) that were available for renogram parameters analysis (Fig. 1). The kidneys were divided into 5 groups; 4 pediatric (2–5, 6–9, 10–13 and 14–18 years old) and adults (19–71 years old). The number of kidneys versus patient age is shown in Figure 1.

Radiopharmaceuticals and imaging

The scintigraphic examination was performed using a dual-head gamma-camera, immediately after the intravenous injection of ^{99m}Tc-EC prepared using a sterile cold kit (Institute of Isotopes, Budapest, Hungary). The dose range from 18,5MBq to 111MBq, containing 0.3–0.7 mg of the ^{99m}Tc-EC complex [13]. The amount of radioactivity for infants and children was based on their body weight [14]. Study was performed without furosemide injection, and the patients were asked to void before image acquisition. The ^{99m}Tc-EC complex was administered intravenously as the acquisition on gamma camera was launched.

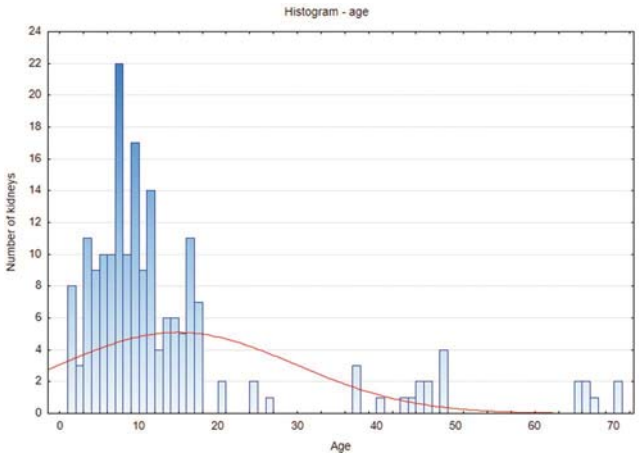

Figure 1. Number of tested healthy kidneys versus the age of patients

Table 1. Criteria for healthy kidney selection

All consecutive kidneys were considered functionally efficient based on the following criteria:
Clinical criteria: • children not younger than 2 years old [9]; • no history of any diseases of the urinary tract or the selected kidney; • blood levels of urea and creatinine within normal ranges according to the reference values provided by the laboratory; • in ultrasound, selected kidneys were typically located with normal shapes and sizes; • no signs of dilated pelvis or calices, cysts, cortical defects, or other morphological abnormalities.
Scintigraphic criteria: • smooth renal outer contour in the parenchymal phase; • the calyx-pelvis system is not enlarged; • even distribution of the radioactive substance in the kidney parenchyma; • a gradual, slow evacuation of the calyx and pyelone system is observed; • no retention of the radiotracer at the end of the observation; • ranographic curve correct in the visual assessment [6]; • no single kidney; • no use of furosemide or furosemide administered after the excretory phase.

The study was performed using the Symbia T16 SPECT/CT hybrid gamma camera (Siemens, Erlangen, Germany). The low-energy high-resolution collimator was used. The analyzer window was set at 140 keV. The data were collected on a 128 × 128 matrix. The examination was carried in the posterior-anterior projection, having a kidney in the field of view. In the first minute of the study, the scintigraphy was recorded with a time resolution of 2 seconds (30 projections) and during the remaining 20 minutes with a time resolution of 30 seconds (40 projections). The test time was 21 minutes in total. The percentage uptake of both kidneys (split function) was determined automatically using the method of comparing fields under the time-activity curves after extrarenal background correction [9].

The manual postprocessing and the designation of the regions of interest (ROI) were performed with the use of the dedicated built-in software provided by Syngo (version: SymbianetVA10D) on a generic protocol. The renographic curves were drawn for each

ROI, for both kidneys separately. The drawing of ROI was performed for the entire kidney and the area between the kidneys (blood background) [7].

Statistics

Peak time (Tmax) was defined as the minutes from the ^{99m}Tc-EC injection to the point of highest radioactivity over the kidney. Half-clearance time (T1/2) was calculated from the peak time to the point when half of the radioactivity in the kidney disappeared. The split function represented the ratio of one kidney function to the global renal function as a percentage of all measured activity [15].

Statistical analysis was performed using the Statistica 13.1 software (Stat Soft, Poland). All values derived in this study are shown as the mean value ± coefficient interval (95%). The distribution was examined using the Shapiro–Wilk test of normality. Dependencies between the parameters were estimated using the nonparametric Mann-Whitney U test for two independent samples and the Kruskal-Willis test for more than two independent samples. The statistical significance was defined as $p \leq 0.05$. Pearson linear correlation coefficients were applied.

Ethics

Every patient signed an informed consent from. The study protocol and informed consent forms were approved by the ethics committee of the Bioethical Council, Medical University of Lublin, Poland.

The tests were tolerated well by all patients.

Results

Mean values, standard deviation (SD) and coefficient interval (CI) of the renographic curve parameters for all kidneys obtained in this study are listed in Table 2. Normal values [here assumed to be the mean value (mean SD)] of Tmax is 2.85 min [0.58 min] and T1/2 is 8.7 min [1.83 min]. The values obtained in the pediatric study are different and age-dependent. They are also given in Table 2. The normal value of Tmax is 2.81 min (0.59 min) and that of T1/2 is 8.63 min (1.86 min).

A comparison of Tmax, T1/2 in different age groups (5 groups: 2–5, 6–9, 10–13, 14–18, 19–71 years) shows that age has no significant effect on both parameters: Tmax ($p = 0.061$) and T1/2 ($p = 0.386$). In the pediatric groups (4 groups: 2–5, 6–9, 10–13 and 14–18 years), too, the differences are insignificant: Tmax ($p = 0.07$) and T1/2 ($p = 0.192$).

The normal values of renographic curve parameters for both sexes and sides are given in Table 3. A comparison of Tmax, T1/2 for female and male patients shows that the sex of the patient does not affect Tmax ($p = 0.339$) and T1/2 ($p = 0.256$). In the case

Table 2. Normal values of the renographic curve parameters Tmax, T1/2 depending on the total number of tested kidneys, pediatric study, and age group

	Age group	n	Min [min]	Max [min]	Median [min]	Mean [min]	± SD	conf. interval (95%)	conf. interval (95%) lower	conf. interval (95%) upper
Tmax	all	194	1.50	4.50	3.00	2.85	0.58	1.16	1.69	4.00
	pediatric	166	1.50	4.50	3.00	2.81	0.59	1.16	1.65	3.97
	2–5 years	31	1.50	4.00	2.50	2.68	0.53	1.09	1.59	3.77
	6–9 years	54	2.00	4.00	2.50	2.68	0.56	1.14	1.54	3.81
	10–13 years	44	2.00	4.00	2.50	2.87	0.60	1.23	1.65	4.10
	14–18 years	37	2.00	4.50	3.00	3.05	0.59	1.21	1.85	4.26
	19–71 years	28	2.00	4.50	3.00	3.06	0.53	1.12	1.94	4.17
T1/2	all	194	5.15	14.90	8.50	8.70	1.83	3.61	5.10	12.32
	pediatric	166	5.15	14.90	8.50	8.63	1.86	3.71	4.90	12.32
	2–5 years	31	5.50	14.90	8.70	8.93	1.98	4.11	4.82	13.04
	6–9 years	54	5.15	12.10	7.70	7.99	1.65	3.34	4.65	11.33
	10–13 years	44	6.10	13.50	8.58	8.98	1.82	3.72	5.27	12.70
	14–18 years	37	5.40	14.10	8.70	8.91	1.93	3.96	4.95	12.87
	19–71 years	28	6.00	12.80	9.24	8.96	1.63	3.40	5.68	12.48

Table 3. Comparison of normal values of the renographic curve parameters Tmax, T1/2 for both sexes and sides

	Age group	Female	Male	Left kidney	Right kidney
Mean Tmax [min]	all	2.88	2.80	2.86	2.84
	children (2–18)	2.85	2.75	2.82	2.80
	adults	3.17	2.97	3.03	3.08
Mean T1/2 [min]	all	8.57	8.88	8.74	8.64
	children (2–18)	8.42	8.97	8.66	8.61
	adults	9.82	8.52	9.22	8.89

of children, the differences between Tmax and T1/2 for female and male patients are Tmax ($p = 0.408$) and T1/2 ($p = 0.075$). T1/2 correlates with Tmax ($p = 0.004$). The correlation between these values depending on the age group is ($r = 0.604$) for all kidneys and ($r = 0.59$) for children.

Discussion

We have developed the standards of dynamic renal scintigraphy parameters for the nuclear medicine department in which the study was conducted. This will facilitate the preliminary assessment of kidney health, which is particularly useful in the study of children. At the same time, to obtain comprehensive results, a more accurate visual assessment of the images is necessary to exclude focal defects in the parenchyma as they may be invisible on the renographic curve. The Tmax and T1/2 parameters were evaluated. The split function ranging from 45% to 55% for each kidney was considered only in the case of patients having both kidneys normal.

Comparing the differences between the obtained calculated parameters one can observe that:

1. The normal value of the secretory function parameter does not significantly depend on age. The changes developing in the kidneys with age are related to all kidney structures. First of all, a reduction in the size and weight of the organ can be observed. The study shows that the size of the glomeruli does not change with age, however, the number of cells in the glomeruli decreases to a significant degree. This may eventually lead to renal function impairment [1]. The scatter plot in Figure 2 shows both parameters tend to slightly increase with age (which demonstrates a slight increase in the parameters for older patients), but the correlation is under the assumed significance level of $p = 0.05$. This indicates that there is no need to establish separate norms for adults and children. Only healthy kidneys were taken into consideration, so we do not obtain any information about differences in kidney diseases between adults and children.

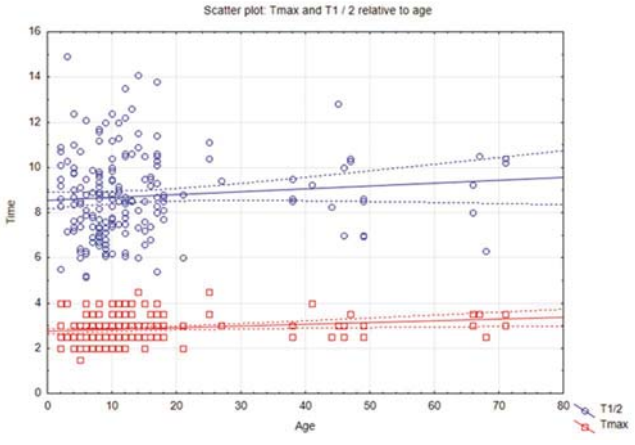

Figure 2. Scatter plot of secretion and extraction times (Tmax and T1/2) versus the age of patients in ^{99m}Tc-EC dynamic renal scintigraphy

2. In terms of the sex, globally, there are no significant differences for any parameters, as can be concluded from Table 3, even though that there are differences in the structure and function of the kidneys depending on the gender [16].
3. Globally, there are no significant differences between the sides.
4. There is a strong positive correlation between the excretory function parameter and the secretory function parameter for normal kidneys.

Compared to Van Nerom first evaluation on healthy volunteers from 1993 [11], calculated times for adults are slightly different (our results are given in Tab. 3). The Tmax mean value [min] for the left and the right kidney is 3.3 and 5.0 (Van Nerom) vs. 3.03 and 3.08. The T1/2 mean value [min] for the left and the right kidney is 6.5; 10.0 (Van Nerom) vs. 9.22; 8.89. The differences might result from the size of the test group; the above-mentioned study was conducted on a group of only six adult male volunteers (averaging 27.5 years old), while the present study was conducted on 27 adults (F/M: 9/10; aged 21–71; averaging 43.8 years old). In a 1997 study examining 4 children with normal kidneys and 15 children with various renal disorders [12], the calculated renal function parameters for normal kidneys were found to be similar for ^{99m}Tc-EC and ^{99m}Tc-MAG3. The mean Tmax values (min) were 3.2 and 3.1, respectively, and the mean T1/2 values were 6.3 and 6.4, respectively. Again, the difference might stem from the size of the test group. The differences might also depend on the group selection because in the aforementioned study both normal kidneys and kidneys with various renal disorders were examined.

Compared to the Sohaib data from 2013 [15], the calculated function parameters are much lower. More specifically, the Tmax mean value (min) is 4.6 (Sohaib) vs. 3.06, while the T1/2 mean value [min] is 14.5 (Sohaib) vs. 8.96. Again, the research group is smaller and contains only adult male volunteers (averaging 30 years old). This difference may also result from the fact that all curves were considered correct in the data collecting process. There are also significant differences in the parameters of kidney perfusion that were obtained in the studies conducted with other dynamic renal scintigraphy radiopharmaceuticals such as ^{99m}Tc-MAG3 [15, 17].

International Scientific Committee of Radionuclides in Nephrourology (ISCORN) noted that the final urine flow depends on the hydration state. Dehydration can cause false-positive results and hydration degrees significantly affected renogram pattern and renal parameters [18]. When the ROI was placed over the whole kidney, the parameters that increased statistically significantly in the dehydrated state where Tmax, T1/2 [5, 17, 19]. The quality of dynamic renal imaging can be degraded by a full bladder, the patient should void before image acquisition, to promote drainage, or it can influence renal function parameters [5]. Our study was performed without furosemide injection, and the patients were asked to void before image acquisition.

In this study mean values, standard deviation (SD) and coefficient interval (CI) were used. The use of the standard error of the mean (SEM) should be limited to inferential statistics where the author explicitly wants to inform the reader about the precision of the study and how well the sample truly represents the entire population. In terms of diagrams and figures, too, the use of SD is preferable to the SEM. To determine the standard range for the biological parameter, it is proposed that the coefficient interval

(the level of confidence of 95%) should be used to ensure that the deterministic parameter is captured by the interval [20].

A great advantage of this study is that it concerns the problem that has not been widely discussed in the literature and that it was conducted on a larger research group. Although the ^{99m}Tc-MAG3 dynamic renal scintigraphy has been investigated by many studies, the standards of ^{99m}Tc-EC dynamic renal scintigraphy have not yet been sufficiently defined. At the same time, it should be noted that the calculated norms for the analyzed parameters may disagree with the standards obtained in other research centers, due to the subjectivity of ROI selection and renographic curve correctness assessment. The results of this study can be a starting point for further research on the establishment of renographic curve parameter norms for patients with particular kidney diseases.

The best cutoff value to separate normal from abnormal values would be obtained by comparing results for normal and diseased populations. In practice, it is often difficult to generalize such a comparison because the degree of abnormality can depend on the selection criteria used to define the disease population. Any value lying outside of the fifth or 95th percentile is considered abnormal. Values outside the lower range of normal are likely to represent a processing problem rather than an abnormality of renal function.

Conclusions

In this study, we proposed the range of normal renal function parameters for ^{99m}Tc-EC dynamic renal scintigraphy. The study has demonstrated that the normal value of the secretory and excretory function parameter does not depend on age, and that, globally, there are no differences between the sexes and the sides for any parameter.

Conflicts of interest

There are no conflicts of interest.

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