Preliminary assessment of inter- and intraobserver reproducibility, and normative values of renal mean transit time (MTT) and parenchymal transit time (PTT) for 99mTc-etylenodicysteine

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Abstract

BACKGROUND: The clinical significance of MTT and PTT, determined by deconvolution of renographic curves, is arguable. Their usefulness in diagnosis of obstructive uro- and nephropathy, renovascular hypertension and monitoring of transplanted kidneys is pointed out, but susceptibility of deconvolution methods to errors resulting from “statistical noise” is also stressed. So far there are no reports on normative MTT values for 99mTc-EC, although such values were already determined for 131I-OIH, 99mTc-DTPA and 99mTc-MAG3. The aim of this study is an assessment of inter- and intraobserver reproducibility of MTT and PTT for 99mTc-EC, and determination of normative values for these parameters.

MATERIALS AND METHODS: 31 patients (17 women and 14 men aged 19–75, average 44 years) referred for dynamic renal scintigraphy with: unilateral flow impairment (11), unilateral nephrolithiasis (2), control after unilateral lithotripsy (4), moderate hypertension (demographically with > 99% probability of primary hypertension) (4), suspected cirrhosis of one kidney (3), future kidney donors (3), control after abdominal injuries (3), incontinence (1).

42 functionally efficient kidneys were included in the study. Criteria for recognition of a kidney as functionally efficient were:
— no earlier history of renal disease, signs of renal damage in basic blood and urine tests, or abnormalities in ultrasonography;
— normal result of dynamic renal scintigraphy (in terms of sequential images and renographic curve).

MTT and PTT values were determined independently by two operators, using a matrix method for deconvolution of renographic curves.

RESULTS: Differences between mean MTT and PTT from two studies by one operator were insignificant and those values were closely correlated (r = 0.99 and r = 0.97, respectively). Differences of values obtained by both operators were practically insignificant for MTT (r = 0.93), and significant for PTT (r = 0.81 and p < 0.001). These differences do not disqualify that processing method. The upper limits of normative values of MTT and PTT were based on the results from first study performed by more experienced operator — 200 s and 170 s, respectively.

CONCLUSIONS: The procedure of processing dynamic renal scintigraphy used in this study is reproducible. Normative values of MTT and PTT for 99mTc-EC were established as 200 s and 170 s, respectively. An attempt to optimize and standardize the technique of determining parenchymal ROI in a matrix deconvolution method, followed by an evaluation of clinical usefulness of these parameters in the diagnosis of chosen renal function impairments would be a logical continuation of this initial research.

KEY words: adult, humans, radioisotope renography, reproducibility of results, radiopharmaceuticals, technetium Tc 99m-ethylenedicyisteine

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Background

Complexity of the renal function makes it difficult to cover its whole range with a single diagnostic procedure. Scintigraphic methods are limited to the assessment of the two arbitrary renal functions. Those are: "uptake function", that is the ability of a kidney to absorb a specific radiopharmaceutical from the bloodstream and "transit function", that is the ability to transport an absorbed tracer through the kidney parenchyma to the urinary tract. Dynamic renal scintigraphy, used for many years in the diagnosis of the condition of kidneys, allows the assessment of both of these functions using radiopharmaceuticals such as $^{131}$I-OIH, $^{99m}$Tc-DTPA, $^{99m}$Tc-MAG$_3$ and the most recently introduced — $^{99m}$Tc-EC.

Dynamic renal scintigraphy allows the evaluation of these functions based on a qualitative assessment of sequential scintigraphic images and the shape of the renographic curves. Additionally, basic quantitative parameters are also calculated — the relative participation of each kidney in their overall function (split function) and times: of achieving maximum activity of the radiopharmaceutical in the kidney — $T_{max}$ and decrease of that activity to half of the maximum — $T_{1/2}$. Some other quantitative parameters are also used, for example: ratio of activity in the kidney in the 20th minute to maximum activity (R20/max), or to activity in the 3rd minute (R20/3), or the ratio of the maximum activity to activity in the 890th second (ER — excretion ratio) [1–3]. For a more thorough analysis of the function of each kidney and urinary tract, parametric images of renal clearance function [4–6], ureteral peristalsis [7] and others [8–10] are also generated. Moreover, after processing of the scintigraphic data, additional parameters concerning the transport of the radiopharmaceutical through the entire kidney — MTT (Mean Transit Time) and its parenchyma — PTT (Parenchymal Transit Time), can be obtained.

MTT and PTT can have an important role in the diagnosis of obstructive uro- and nephropathy [11, 12], renovascular hypertension [12–14] and in monitoring the function of the transplanted kidney [15, 16]. The most common methods used to determine the values of these parameters are based on the deconvolution of renographic curves and blood activity curve. Some authors, however, point out an uncertainty of the time parameters calculated by deconvolution, caused by a susceptibility of the impulse response function to the noise from the stochastic nature of radioactive decay and radiation detection [17, 18]. For that reason, Rutland et al. [19] and Sámal et al. [20] presented methods for determining MTT and PTT not relying on deconvolution of renographic curves. According to Fleming's comparative analysis of this parameters determined by means of deconvolution and a method based on Rutland’s theory their similar usefulness for the calculation of renal transit time parameters has been shown [21]. On the other hand, the method proposed by Sámal et al. [20] based on factor analysis, requires the acquisition of sequential images in short time intervals, which in turn requires administering the patient higher activity of the radiopharmaceutical. Therefore, MTT and PTT are most frequently measured with deconvolution methods based on the matrix algorithm or Fourier transformation [21–23].

It is expected that MTT and PTT determination techniques, as well as other research methods, meet the requirements of inter- and intraobserver reproducibility. Therefore, in this study, these values for the procedure based on the matrix deconvolution algorithm were evaluated.

The upper limit of normative values of MTT and PTT is also considerably significant (lower limit is not taken into account, since shorter transit time through kidneys is not important from a clinical point of view). Such values were determined for $^{131}$I-OIH [24], $^{99m}$Tc-DTPA [25–27] and for $^{99m}$Tc-MAG$_3$ [3, 28], both based on groups of healthy volunteers as well as patients with kidneys considered as functionally efficient. So far there are no reliable normative values of MTT and PTT for $^{99m}$Tc-EC. Gupta et al. [29] only determined the value of PTT, but just on a group of five healthy volunteers. Among nephrothropic radiopharmaceuticals, $^{99m}$Tc-EC has favourable pharmacological properties (a high extraction rate), which make it especially useful and applicable for dynamic renal scintigraphy [30–32]. However, different renal extraction mechanism of $^{99m}$Tc-EC than of $^{99m}$Tc-DTPA and $^{99m}$Tc-MAG$_3$, and different proportions of its filtration and secretion than of $^{131}$I-OIH, make it necessary to determine separate normative values of MTT and PTT for these radiopharmaceuticals.

The purpose of this study is to evaluate the inter- and intraobserver reproducibility of the procedure, and determine normative values of MTT and PTT for $^{99m}$Tc-EC.

Materials and methods

Dynamic renal scintographies performed at our department in years 2011–2013 were analysed retrospectively. Kidneys were considered functionally efficient based on the following criteria:

- patients had routine urinalysis within normal limits and blood levels of urea and creatinine within normal ranges according to the reference values provided by the laboratory;
- they had no history of any diseases of the urinary tract or the selected kidney;
- in ultrasound, selected kidneys were typically located and had normal shapes and sizes. There were no signs of dilated pelvis or calices, cysts, cortical defects, or other morphological abnormalities;
- the result of dynamic renal scintigraphy of the selected kidney in terms of sequential images and renographic curve, assessed independently by two physicians, was normal (that includes the split function of the kidney $>45\%$, $T_{max} \leq 300\;s$ and $T_{1/2} \leq 600\;s$). Based on the above criteria, 42 kidneys regarded as functionally efficient were selected in 31 patients — 17 women and 14 men aged 19–75 years (44 years on average).

Those patients were referred for dynamic renal scintigraphy with:

- suspected unilateral outflow impairment (all confirmed impairments were minor and did not require a diuretic test — 11 patients) (only contralateral kidney was selected);
- suspected unilateral nephrolithiasis (2 patients) (only contralateral kidney was selected);
- control after unilateral lithotripsy (no sooner than 1 year after therapy — 4 patients) (only contralateral kidney was selected);
- moderate, freshly diagnosed hypertension, demographically with $>99\%$ probability of primary hypertension (study without captopril — 4 patients) (both kidneys were selected);
- suspected cirrhosis of one of the kidneys (excluded after renal scintigraphy — 3 patients) (only contralateral kidney was selected);
- qualification of future kidney donors (3 patients) (both kidneys were selected);
The study was started at the time of intravenous administration of 111 MBq (3 mCi) of 99mTc-EC, collecting 60 twenty-second images in matrix 64 × 64 during 20 minutes.

Scintigraphic data processing was performed by drawing regions of interest (ROI) including the heart, the entire kidney, the renal parenchyma (possibly excluding the pelvis and calices) and area between the kidneys (blood background). The ROI for the whole kidney was determined by isocontour at 20% of the maximum counts on the summed images recorded between 2nd and 3rd minute of the study. Other ROIs were drawn manually: for heart — on the first registered image, for renal parenchyma — on summed images from between 14th and 15th minute of the study (avoiding calices and pelvis visible in these images). Then, time-activity curves were drawn for each ROI. Curves were smoothed with a three-point filter with 1–2–1 weight coefficients. Blood background curve was subtracted from the curves for the whole kidney and renal parenchyma (after correction due to ROI size). From these curves, MTT and PTT were determined using the matrix algorithm deconvolution.

In order to assess intra- and interobserver reproducibility of determined values of MTT and PTT, scintigraphic data were processed independently by two operators:

— more experienced (A) — twice, with time interval of about 2 weeks, resulting in two pairs of MTT and PTT for each kidney (MTT A1 and PTT A1; MTT A2 and PTT A2);

— less experienced (B) — once (MTT B and PTT B).

To establish normative values of determined parameters, the value obtained by the operator A in the first study was taken. Their control after abdominal injuries (any damage to the kidneys was excluded by morphological and scintigraphic evaluation — 3 patients); incontinence (1 patient); incontinence (1 patient) (both kidneys were selected).

In all patients, dynamic renal scintigraphy was carried out according to the standard protocol without a diuretic test. Each patient approx. 1/2 h before the test was recommended to drink 500 ml of water and empty the bladder immediately before testing. The study was performed on cameras: Mediso Nucline AP; Infinia Hawkeye 2 and Infinia Hawkeye 4, equipped with low-energy, general purpose collimators (LEGP). During the test, a patient was placed in a supine position. Gamma camera detector was positioned under the patient with the field of view including both the kidneys and the heart. The study was started at the time of intravenous administration of 111 MBq (3 mCi) of 99mTc-EC, collecting 60 twenty-second images in matrix 64 × 64 during 20 minutes.

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— less experienced (B) — once (MTT B and PTT B).

To establish normative values of determined parameters, the value obtained by the operator A in the first study was taken.

### Table 1. Values of basic parameters describing distribution of results acquired by both operators

<table>
<thead>
<tr>
<th>Study</th>
<th>Min.</th>
<th>Max.</th>
<th>Mean</th>
<th>St. dev.</th>
<th>Mean + 2sd</th>
<th>Compared pairs of results</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTT A1</td>
<td>111</td>
<td>214</td>
<td>149</td>
<td>26</td>
<td>201</td>
<td>MTT A1 vs MTT A2</td>
<td>p = 0.87</td>
</tr>
<tr>
<td>MTT A2</td>
<td>105</td>
<td>218</td>
<td>148</td>
<td>26</td>
<td>200</td>
<td>MTT A1 vs MTT B</td>
<td>p = 0.02</td>
</tr>
<tr>
<td>MTT B</td>
<td>97</td>
<td>208</td>
<td>145</td>
<td>25</td>
<td>195</td>
<td>PTT A1 vs PTT A2</td>
<td>p = 0.36</td>
</tr>
<tr>
<td>PTT A1</td>
<td>80</td>
<td>171</td>
<td>128</td>
<td>21</td>
<td>169</td>
<td>PTT A2 vs PTT B</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PTT A2</td>
<td>81</td>
<td>176</td>
<td>129</td>
<td>21</td>
<td>170</td>
<td></td>
<td>0.77</td>
</tr>
<tr>
<td>PTT B</td>
<td>86</td>
<td>150</td>
<td>114</td>
<td>15</td>
<td>145</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In order to assess intra- and interobserver reproducibility, or obtained from the first study by the operator A and the study by the operator B (MTT A1 vs MTT A2 for interobserver reproducibility). For this purpose Student’s t-test for pairs was applied (normality of distributions was verified with Shapiro-Wilk’s test). In addition to statistical significance, practical significance of observed differences was also assessed, using Cohen’s d-coefficient, which is a measure of the effect size, that is — the difference between two mean values of MTT or PTT from different studies divided by a standard deviation for the data. (Formula: $d = (M1 - M2)/SD_{pooled}$, where $M1$ is the mean value of MTT A1 or PTT A1, $M2$ is the mean value of MTT B or PTT B for intraobserver, and MTT B or PTT B for interobserver reproducibility, respectively; while $SD_{pooled}$ is the standard deviation for the samples ($SD_{pooled} = \sqrt{(SD_{A1}^2 + SD_{A2}^2)/2}$).)

It is assumed that $d > 0.8$ indicates significant differences, $0.5-0.8$ — medium, $0.2-0.5$ — small, and $< 0.2$ means that the differences are practically trivial. As an additional measurement of assessment reliability, linear correlation coefficients were applied, similarly for the results obtained in the two studies of the same operator in case of intraobserver reproducibility, and the results obtained by two independent operators for interobserver reproducibility.

Statistical analysis was performed with Statistica 10.0 software.

### Results

Basic parameters of distributions of MTT and PTT values obtained by each of the operators are summarized in Table 1. There were no statistically significant differences between mean values of MTT and PTT from two studies by operator A (respectively $p = 0.87$ and $p = 0.36$). The mean difference between the results did not exceed $1s$. Cohen’s d-coefficients for MTT and PTT were $d = 0.03$ and $d = 0.05$, respectively.

On the other hand, MTT and PTT obtained by operators A and B differed significantly ($p = 0.02$ and $p < 0.001$, respectively). The mean difference between the results was $4s$ for MTT and $14s$ for PTT. Cohens d-coefficients for MTT and PTT amounted to $d = 0.16$ and $d = 0.77$, respectively.

Linear correlation coefficients between MTT and PTT values from two studies by operator A were $r = 0.99$ (Figure 1A) and $r = 0.97$ (Figure 1B), respectively, while for the pairs of values for MTT and PTT obtained by two operators — $r = 0.93$ (Figure 1C) and $r = 0.81$ (Figure 1D), respectively.

Normative values for MTT and PTT for normal kidneys were determined based on the first study performed by operator A. Their...
upper limits were determined as mean values plus two standard deviations (rounded), that is for MTT: $(149 + 2 \times 26) \approx 200 \text{ s}$, and for PTT: $(128 + 2 \times 21) \approx 170 \text{ s}$.

**Discussion**

Lack of significant differences between the mean values of MTT and PTT, and their close correlation in studies performed by the same operator (Figure 1A and 1B) give grounds to consider the processing procedure of dynamic renal scintigraphy used in this work to have high intraobserver reproducibility.

In case of studies performed by two operators, there were statistically significant differences between the mean values of the results. However, for MTT, these differences had no practical significance ($d < 0.2$). Therefore, our method can be considered to have high interobserver reproducibility in this field, which is confirmed by a close correlation between pairs of MTT values obtained by both operators (Figure 1C).

The results were different in case of PTT values obtained by both operators. Their mean values show statistically significant differences with medium size of effect ($d = 0.77$) and the correlation results were not as strict as in the case of MTT, although they were still high ($r = 0.81$, Figure 1D). This suggests that interobserver reproducibility is slightly lower in this field. These differences, however, do not disqualify the processing methods of dynamic renal scintigraphy.

High reproducibility of the results obtained by both operators for the MTT and the differences between the results obtained by these operators for PTT, can be explained by different methods of determining regions of interest for the whole kidney and its parenchyma (Figure 2). Whole kidney ROIs (for determining MTT) were drawn with isocontour with a constant value of 20% of the maximum number of counts in the kidney. This method of determining ROIs is strictly defined and reproducible. Only small, ischemic or

![Figure 1](image1.png)

**Figure 1.** Correlations between values obtained by the same operator in two studies for (A) MTT and (B) PTT — intraobserver reproducibility; and correlations between values obtained by both operators; (C) MTT and (D) PTT — interobserver reproducibility

![Figure 2](image2.png)

**Figure 2A.** ROI for MTT, selected with isocontour with constant value of 20% maximum counts; **B.** ROI for PTT, selected manually
cystic kidneys may cause some problems. On the other hand, parenchymal ROIs (for determining PTT) were drawn manually, so subjective factors could have a significant impact on their shape. Depending on the size of the selected area, it can for example contain smaller or larger share of calices, and that can change the value of determined parameter. Further efforts are necessary to minimize the impact of subjective elements in determination of parenchymal ROIs, by either standardization or automatization of the methods of selecting the ROI. Similar solution was also suggested by Bergmann et al. [33].

Because of the fact that the results of MTT and PTT had high inter- and intraobserver reproducibility (even in case of PTT), they can be used as a basis for determining the upper limits of normative values for these parameters for normally functioning kidneys. Taking into account the values obtained by a more experienced operator in the first study, the upper limit of normal range was assumed to be 200 s for MTT and 170 s for PTT.

In Table 2, mean values of normal MTT and PTT obtained in our work were compared with those obtained by different authors for other radiopharmaceuticals in kidneys considered functionally efficient. It is apparent that mean values of MTT obtained in this work are lower than values obtained both by Piepsz et al. [25] and Rajabi et al. [17] for 99mTc-DTPA, as well as those calculated by Russell et al. [3] and Gonzales et al. [28] for 99mTc-MAG3. On the other hand, they are comparable with values reported by Kenny et al. [24] for 131I-OIH. The mean values of PTT are also lower than those found in literature for 99mTc-DTPA [17] and 99mTc-MAG3 [3, 28]. It is also notable that Gupta et al. [29] obtained surprisingly high normative values of PTT for 99mTc-EC (in 5 healthy volunteers determined PTT was from 125 s to 206 s, on average — 175 s). Differences between MTT and PTT obtained in this work for 99mTc-EC and values of these parameters for other radiopharmaceuticals may result both from methodological factors and different mechanisms of their extraction in nephron. 99mTc-DTPA is a subject only to glomerular filtration. 99mTc-MAG3 is also excreted in only one mechanism — tubular secretion. 131I-OIH on the other hand, is a subject to both glomerular filtration and tubular secretion, just like 99mTc-EC, which can explain similar MTT values obtained for these radiopharmaceuticals.

Conclusions

Obtained results justify the opinion that the procedure of processing dynamic renal scintigraphy studies used in this research to determine the values of MTT and PTT gives reproducible results. Normative values of transit times for 99mTc-EC through the whole kidney and its parenchyma were determined as 200 s and 170 s, respectively. An attempt to optimize and standardize the technique of determining parenchymal ROI in a matrix deconvolution method, followed by an evaluation of clinical usefulness of these parameters in the diagnostics of chosen renal function impairments would be a logical continuation of this initial research.

References


