

## A Comparison Between the Values of Renal Parenchymal Mean Transit Time by Applying Two Methods, Matrix Inversion Deconvolution And, Rutland-Patlak Plot

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**Abstract:** Deconvolution and the Patlak-Rutland plot are two of the most commonly used methods for analyzing dynamic radionuclide renography. Both methods allow estimation of absolute and relative renal uptake of radiopharmaceutical and of its rate of transit through the kidney. Eighteen patients (33 kidneys) were referred for further evaluation by renal scanning. All patients were positioned supine with their backs to the scintillation gamma camera, so that the kidneys and the heart are both in the field of view. Approximately 5-7 m Ci of  $^{99m}\text{Tc}$ -DTPA in about 0.5 ml of saline is injected intravenously and sequential 20 sec frames were acquired; the study on each patient lasts for approximately 20 mins. The time-activity curves of the parenchymal region of each kidney, as well as the heart were obtained for further analysis. The data were then analyzed using deconvolution and the Rutland-Patlak (R-P) plot. The values of the renal parenchymal mean transit time (PMTT) obtained by applying matrix inversion deconvolution method are significantly higher than that obtained by the Rutland-Patlak plot ( $P = 0.013$ ). A strong positive correlation ( $n = 33$ ;  $r = 0.80$ ;  $R^2 = 0.64$ ) was found between the values that obtained by applying the two methods. From a Bland-Altman statistical test that was performed on the results we also found that 94% of the cases (32/33) were within 1.96 SD. We believe that Rutland-Patlak analysis method is expected to be more reproducible than matrix inversion deconvolution method, because the deconvolution technique relies heavily on the accuracy of the first point analyzed (plateau point), as any errors are carried forward into the calculations of all the subsequent points, whereas R-P technique is based on an initial analysis of the data by means of the R-P plot (slope of the first phase) and it can be considered as an alternative technique to find and calculate the renal PMTT.

**Key words:** Matrix inversion deconvolution % Rutland-Patlak plot % Renal parenchymal mean transit time % Renal retention function

### INTRODUCTION

Deconvolution and the Rutland-Patlak (R-P) plot are two of the most commonly used methods for analyzing dynamic radionuclide renography. Both methods allow estimation of absolute and relative renal uptake of radiopharmaceutical and of its rate of transit through the kidney [1].

Gamma camera renography has been used widely for the assessment of renal function over the last 20 years [2]. Many methods have been used to derive quantitative parameters from the measurements [3-6]. The uptake of activity in the kidney before the minimum transit time of the radiopharmaceutical is taken as a measure of renal function. Both relative and absolute uptake may be calculated, the latter can be calculated by relating renal activity to the injected dose [7]. Measurements of the rate

of transit of radiopharmaceuticals through the kidney, such as the peak time [8], mean transit time (MTT) [9] or renal outflow efficiency (ROE) [10], may also be calculated. These parameters are useful in the evaluation of upper urinary tract obstruction, in which they have been shown to improve diagnostic accuracy in patients with impaired renal function [10] and in detecting renovascular hypertension using angio-tension-converting enzyme inhibitor renography [8].

Two of the most commonly used approaches to analysis PMTT are deconvolution [3] and the R-P plot [5]. Both methods attempt to use information on the time variation of the input to the kidney to obtain functional parameters that are independent of the shape of the renogram. Both methods also provide a means of subtraction of intrarenal vascular activity and therefore of estimation of the true renal uptake.

Deconvolution is widely used and considered as the gold standard for the estimation of renal transit time in conditions in which the transit time is assumed to be prolonged, such as renovascular disease, transplant rejection and obstructive uropathy [11-16]. Theoretically at least, using the renogram as the output function and the plasma disappearance curve as the input function, the spectrum of intrarenal transit times can be determined exactly [5,17].

In practice there are many factors which raise questions about the validity of this approach [18,19]. One of these, probably the most important, is the relationship between the spectrum of intrarenal transit times and the duration of data acquisition. It is mathematically obvious that deconvolution can only be applied correctly if the maximal transit time is shorter than the duration of data acquisition. Unfortunately, based on a renogram, one cannot tell whether the maximal transit time is longer or shorter than the acquisition time [20].

Deconvolution analysis has been a useful technique for analyzing organ function in Nuclear Medicine [4,9,21] for a considerable time. There are three established techniques plus one more recent approach [22]. The three main methods are iterative deconvolution (also known as matrix inversion), Laplace Transforms and Fourier Transforms [23].

The iterative deconvolution analysis has been previously applied by many authors [4,16,22,24,25,16], in nuclear medicine investigations. The deconvolution technique has been extensively and most widely applied to renal studies [9,16,24-30].

The aim of the present study was to calculate the values of renal PMTT and to compare between these values by applying two methods, Rutland-Patlak plot (multiple time graphical analysis (MTGA)) [5,23,31,32], and the iterative deconvolution (matrix inversion) using <sup>99m</sup>Tc DTPA [3,4,16,22,24,25,16]. To my knowledge, this research is the first study that compared the values of renal PMTT applying these two methods using <sup>99m</sup>Tc DTPA.

## Theory

### Theory and Derivation of the Retention Function:

The renogram curve, R(t), after corrections for blood and tissue background, is a convolution of the input function from the blood to the kidney, I(t) and the retention function of the kidney, H(t). The main assumption made in this approach is that the kidney can be modeled as a linear, stationary system [33,34.] In practice, the linearity of the system is generally maintained, but the stationarity may often be violated [16].

The technique adopted in this study is that of discrete deconvolution using the matrix algorithm [24]. This algorithm has been applied previously in renal deconvolution [4,16,25]. In this method the linear matrix H is evaluated in a successive manner, starting with H(1) and working through to the final element H(n). Thus, the value of the retention function in the ith interval is given by:

$$H(i) = \frac{1}{I(i)\Delta} [R(i) - \sum_{j=1}^{i-1} I(i-j)\Delta H(j)] \quad (1)$$

Where  $\Delta t$  is the sampling interval which is taken to be 20 s in this study, R and I are obtained by selecting regions of interest over the kidney and the heart, respectively, these values can be used to create time-activity curves for the duration of the study.

Before evaluating H from equation (1), it is necessary to reduce the effect of statistical variations inherent in R and I. This is achieved by applying once a 1: 2: 1 linear non-stationary smooth with appropriate end point constraints to both kidneys and input curves since this has been shown to be an appropriate degree of data filtering in this study [35].

Parenchymal mean transit time, PMTT, derived from the retention function is calculated according to Zieler, [36].

$$PMTT = \sum_{i=1}^n H(i) \Delta t / H \quad (2)$$

**Principles of Gjedde-patlak Analysis:** The original idea of Patlak and Blasberg was to create a model independent graphical analysis method: whatever the tracer is facing in the tissue, there must be at least one irreversible reaction or transport step, where the tracer or its labeled product cannot escape [37].

It is assumed that all the reversible compartments must be in equilibrium with plasma, i.e. the ratio of the concentrations of tracer in plasma and in reversible tissue compartments must remain stable. In these circumstances only the accumulation of tracer in irreversible compartments is affecting the apparent distribution volume. In practice, this can happen only after the initial sharp concentration changes when the plasma curve descends slowly enough for tissue compartments to follow [37].

When the steady state is achieved, the Gjedde-Patlak plot becomes linear. The slope of the linear phase represents the net transfer rate K (influx constant). To make it simple, K represents the amount of accumulated tracer in the kidney to the amount of tracer that has been available in plasma [37].

The y axis of the plot represents an apparent distribution volume that is the ratio of activities of tracer in the kidney and in plasma. The x axis represents the normalized plasma integral, that is the ratio of the integral of plasma activity and the kidney activity [22,23,37].

**The Patlak Plot Is Given by the Following Expression:**

$$\frac{C_{Tissue}(t)}{C_{plasma}(t)} = K \frac{\int_0^t C_{plasma}(u) du}{C_{plasma}(t)} + V$$

This means that the measured kidney activity is divided by plasma activity and plotted at a "normalized time" (integral of input curve from injection divided by instantaneous plasma activity). For systems with irreversible compartments, this plot will result in a straight line after sufficient equilibration time (Figure 3). The slope and the intercept must be interpreted according to the underlying compartment model. For the 99m Tc-DTPA, the slope represents the kidney uptake rate, while the intercept V equals  $V_0 + vB$  with the distribution volume  $V_0$  of the reversible compartment C and the fractional blood volume  $vB$  [38].

For every scintigraphic examination, the renal PMTT of <sup>99m</sup>Tc-DTPA was calculated twice, by applying the two methods Patlak-Rutland plot [31,32] and deconvolution (matrix inversion) using the same operator.

A Rutland-Patlak plot [3,9] is applied to the first few minutes of the renal and blood curves. The intercept of that plot (I) allows completion of the background subtraction process and the slope (M) indicates what proportion of the blood curve is entering the kidney each second (Figure 3).

The R-P plot starts with an initial value and rises up with a slope. The first proof of the R-P plot [39] actually demonstrated that the initial value was equal to the blood background subtraction factor I (the interception of the straight line with y-axis as shown on Figure 3) and that the slope was similar to the uptake constant H(1) (the plateau value as shown on Figure 2).

The value of the uptake rate can be calculated from the slope of the straight line In the first part of the R-P plot of the renogram (as shown on Figure 3), for this patient the slopes are equal to 11%/min for the left kidney and is equal to 17%/min for the right kidney. Whereas the values of the uptake rate obtained by applying the deconvolution method are equal 14%/min and 15%/min for the left and right kidneys respectively, which are equal the value of the plateau of the retention function (as shown on Figure 2).

The value of the renal PMTT is calculated from the two phases of the R-P plot (Figure 3) by applying the following formula:

$$PMTT \text{ (min)} = (Y-I) / M \text{ (minG}^1\text{)}$$

Where

Y = Average value of the points that form the second phase of the R-P plot.

I = Intrarenal vascular activity which corresponds to the interception of first phase of the R-P plot with Y-axis as shown on Figure 3.

M = Uptake rate (minG<sup>1</sup>) which corresponds to the slope of the first phase of the R-P plot.

## MATERIALS AND METHODS

Eighteen patients (33 kidneys) were referred for further evaluation by renal scanning. Eight kidneys were diagnosed to be obstructed by both radiological investigations (intravenous pyelo-graphy) and diuretic renography. As a part of the preparation procedure, the patient should be well hydrated and the urinary bladder is emptied before the study. All patients were positioned supine with their backs to the scintillation gamma camera, so that the kidneys and the heart are both lie in the field of view.

The camera used in this investigation is a Siemens type camera with 16" diameter NaI (TI) crystal used in conjunction with a high-sensitivity parallel-hole collimator. Approximately 5-7 m Ci of 99m Tc--DTPA in about 0.5 ml of saline is injected intravenously and sequential 20 sec frames are stored in a computer equipped with data analysis software. The study on each patient lasts for approximately 20 mins. The time-activity curves of the parenchymal region of each kidney, as well as the heart were obtained for analysis.

The data were then analyzed with deconvolution and the R-P plot. Both deconvolution and R-P plot approaches applied for the assessment of renal PMTT, are based on the assumption that up to a given time after injection, corresponding to the minimum transit time, there is no output of activity from the renal region of interest (ROI) [35].

## RESULTS

Table 1 represents the values for the renal PMTT obtained by the matrix inversion deconvolution and Rutland-Patlak plot methods.

Table 1: Renal PMTT obtained by applying matrix inversion deconvolution and Rutland-Patlak methods

Kidney no.	A	B	(A+B)/2	A-B
1	4.47	3.51	3.99	0.96
2	4.07	3.57	3.82	0.5
3	4.58	3.21	3.895	1.37
4	4.84	3.24	4.04	1.6
5	4.03	4.25	4.14	-0.22
6	3.7	2.57	3.135	1.13
7	4.33	6.06	5.195	-1.73
8	4.1	4.69	4.395	-0.59
9	5.14	4.22	4.68	0.92
10	3.42	2.48	2.95	0.94
11	3.59	2.1	2.845	1.49
12	5.22	4.53	4.875	0.69
13	8.06	5.61	6.835	2.45
14	4.77	3.66	4.215	1.11
15	6.45	3.11	4.78	3.34
16	7.72	6.35	7.035	1.37
17	6.92	4.86	5.89	2.06
18	4.09	3.82	3.955	0.27
19	3.58	3.86	3.72	-0.28
20	6.3	6.46	6.38	-0.16
21	4.84	3.89	4.365	0.95
22	5.88	4.08	4.98	1.8
23	5.63	3.94	4.785	1.69
24	4.92	3.24	4.08	1.68
25	3.61	1.86	2.735	1.75
26	4.08	4.25	4.165	-0.17
27	4.75	4.78	4.765	-0.03
28	6.15	5.62	5.885	0.53
29	4.85	3.48	4.165	1.37
30	8.56	5.8	7.18	2.76
31	5.85	3.6	4.725	2.25
32	8.39	5.88	7.135	2.51
33	10.86	10.37	10.615	0.49
Mean ±	5.39	4.33	4.86	1.05
SD	1.74	1.61	1.68	1.08

A = Renal PMTT (in min) obtained by applying matrix inversion deconvolution method.

B = Renal PMTT (in min) obtained by applying R-P plot method.

Figures 1 and 2 represent the renograms for left and right kidneys for one patient and renal retention functions for these two kidneys obtained by applying iterative deconvolution (matrix inversion) method.

Figure 3 demonstrates renal Rutland-Patlak plot for the two kidneys, which represents the relationship between the values of (the radioactivity (integrated values in the blood (region of interest around the heart)) / (the radioactivity in the blood (region of interest around the heart)) during certain defined time), as x-axis and the values of the radioactivity in the kidney region of interest during certain defined time/radioactivity in the blood for the same defined time, as y-axis.

Figure 4 demonstrates the relationship between the values of the renal PMTT obtained by applying R-P method and the iterative deconvolution (matrix inversion) method. The regression equation of the Patlak-Rutland against iterative deconvolution (matrix inversion) was

$$Y = 0.74 X + 0.35 (r = 0.80).$$

**Results (Statistical Analysis):** The scintigraphy PMTT values determined by Rutland-Patlak method and by the iterative deconvolution (matrix inversion) method, were further analyzed to the method of Bland-Altman, which is a supplementary method to compare two different methods when the true value is unknown. The data was plotted as scatter plot of the mean values versus the difference of both calculations (Figure 5). A plot of the mean of kidney PMTT function calculations obtained by applying the two methods on 32 <sup>99m</sup>Tc-DTPA renography

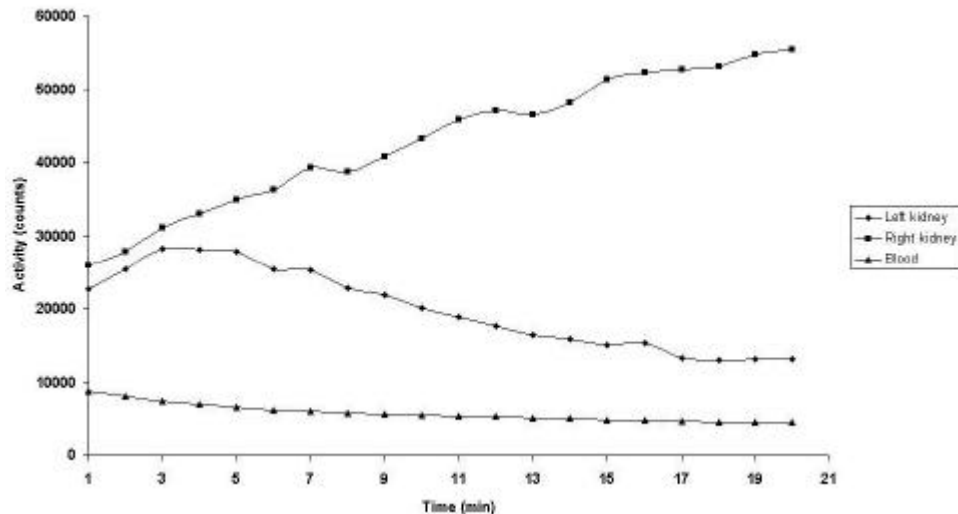


Fig. 1: Renograms for left (normal) and right (obstructed) kidneys.

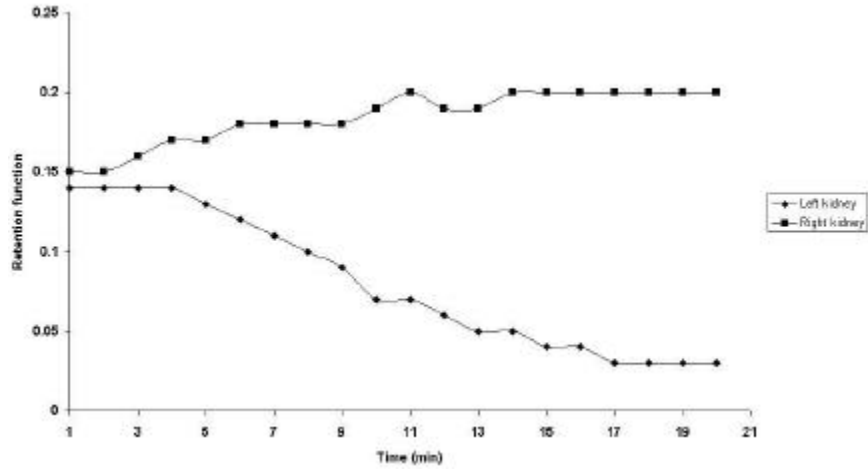


Fig. 2: Renal retention function obtained by applying iterative deconvolution (matrix inversion) method, for left and right kidneys

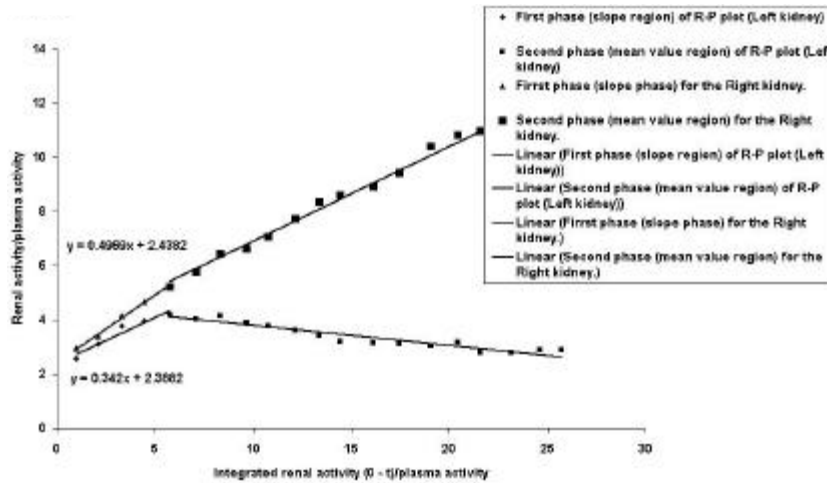


Fig. 3: Renal Rutland-Patlak plot of the all portions of the renograms for left and right kidneys

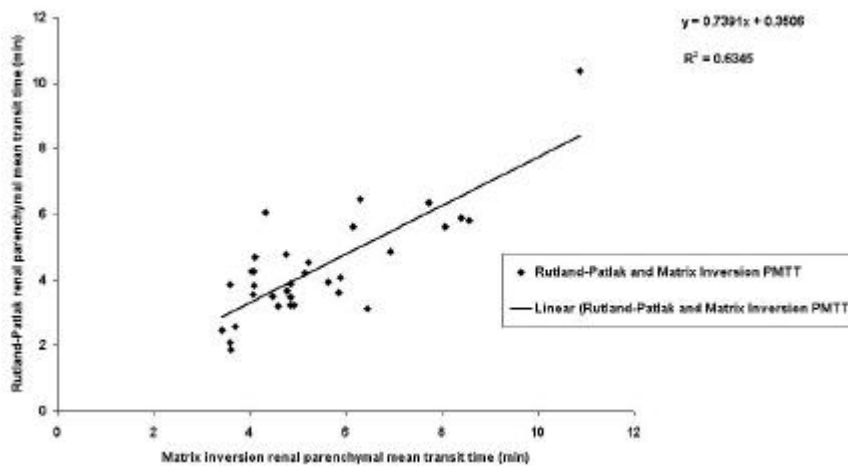


Fig. 4: Scatter plots of renal PMTT determined by Rutland-Patlak method and by the iterative deconvolution (matrix inversion) method

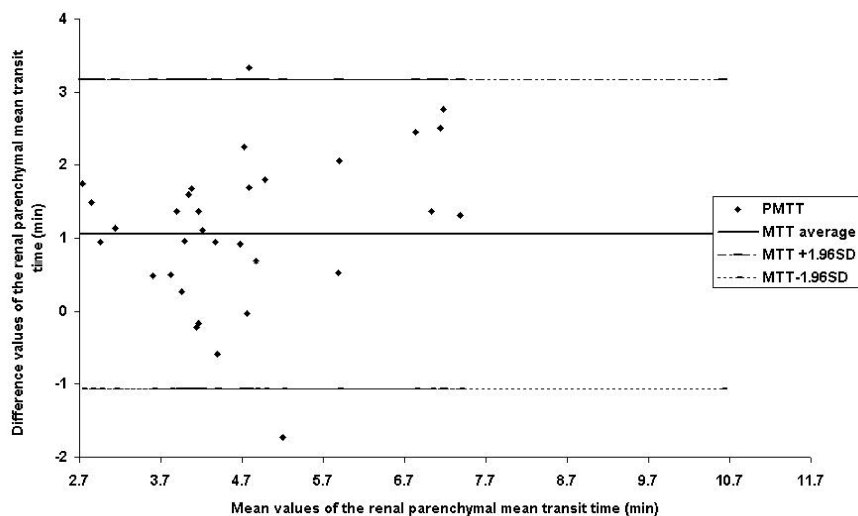


Fig. 5: Bland-Altman analysis. Scatter plots of the mean renal PMTT of the two methods, as the x-axis; against the difference in renal PMTT by Rutland-Patlak method and the iterative deconvolution (matrix inversion), as the y-axis. The solid line indicates the mean difference and the dotted lines indicate the 95% of agreement (1.96 SD).

(horizontal axis), versus the differences in the two calculations (vertical axis). The horizontal solid lines (as shown on Figure 5) indicate the mean difference between the two calculations. The horizontal dashed lines indicate the 95% limits of agreement (mean  $\pm$  1.96 SD). Ninety four percent of the values in the study (31 cases from 33 cases) were within limits of agreement.

As shown in Table 1, the values of the renal parenchymal mean transit time (PMTT) obtained by applying matrix inversion deconvolution method are significantly higher than that obtained by the Rutland-Patlak plot ( $P = 0.013$ ). A strong positive association ( $n = 33$ ;  $r = 0.80$ ;  $R^2 = 0.64$ ) was found between the values that obtained by applying the two methods (Figure 4).

## DISCUSSION

Deconvolution and the R-P plot have been widely used for analysis of renography, each enabling the derivation of renal PMTT corrected for vascular background contribution. M. Rutland [1] have shown that the two methods for uptake measurement are theoretically equivalent, in this article the two methods have validated in practice in a series of 33 renograms that cover a wide variety of ages (15-63 year).

Theoretically, the deconvolution method is an ideal method for the estimation of renal transit [16,40-42]. In practice, however, there are many physiological and

technical factors that hamper the proper application of deconvolution analysis to the renogram [10,19]. Indeed, the conditions that need to be met for deconvolution are not entirely fulfilled. The linearity of the system is not respected when the precordial curve is used as the input function, as it differs from the true plasma curve. The required stationary condition, on the other hand, is violated by changes in renal emptying due to back-pressure of the bladder. An abrupt change in urine flow due to the injection of a diuretic during the acquisition totally invalidates the deconvolution analysis [20].

The R-P plot has now been around for over twenty years, which poses the question of why it has taken so long for this relationship to be made evident? There are two likely reasons. Firstly, that the other forms of deconvolution were available and so there was no great pressure to look for alternatives. The second is that in many cases the R-P plot did not appear to have a level, but actually appeared to decline once tracer started to leave the organ. This will occur when the blood curve being used is not a true measure of arterial blood. That will occur in the later stages of externally measured blood curves when there is an excess of counts due to soft tissue activity also being measured in the "blood" curve. It is possible that looking at the later stages of the R-P plot is a way of actually seeing how truly the externally measured blood curve matches the input function to the organ [23].

The reasoning behind this approach is that in producing the R-P plot, both the content function and the integral of the input function are divided by the input function (ie blood curve) and this has the effect of producing data equivalent to that which would be produced if the input function did not vary (i.e. if there were a constant blood level of tracer) [23].

The calculation of PMTT depends mainly on the first point of the retention function for the matrix inversion deconvolution method and the slope of the straight line for the first phase of the R-P method. We believe that the probability of the error in finding the first point by the first method (which depends on the plateau of the retention function), can't be easily determined, especially for kidneys that function abnormally as shown on figure 2, whereas the value of the slope which is determined from the straight line (that represents the first phase of the R-P plot), can be accurately and easily determined as shown on Figure 3. So the R-P method may be expected to be more reproducible than the matrix inversion deconvolution method.

The deconvolution technique (the iterative method) relies heavily on the accuracy of the first point analyzed, as any errors are carried forward into the calculations of all the subsequent points, whereas Patlak-Rutland technique is based on an initial analysis of the data by means of the R-P plot [31,39].

The conventional deconvolution methods are iterative (or matrix inversion) deconvolution; or using either Laplace or Fourier transforms. Whichever method is used, all are very sensitive to small variations in the input data, making it difficult to prevent large errors developing. Also, all these conventional methods first generate a retention function and then use that retention function to measure the uptake rate from the plateau height, from the uptake rate and the retention function, the renal PMTT can be calculated [22].

In R-P plot the tracer concentration curves of tissue region-of-interest and arterial plasma are transformed and combined into a single curve that approaches linearity when certain conditions are reached. The data could be plotted in a graph and a line can be fitted to the linear phase. The slope of the fitted line represents the net uptake rate of the tracer or volume of distribution [11]. The graphical analysis methods are independent of any particular model structure [20].

## CONCLUSIONS

There was a strong correlation between renal PMTT values measured by Rutland-Patlak and iterative

deconvolution methods; however reported matrix inversion deconvolution values were significantly higher than Rutland-Patlak values.

Whichever deconvolution methods is used, all are very sensitive to small variations in the input data, making it difficult to prevent large errors developing. Also, all these conventional methods first generate a retention function and then use that retention function to measure the uptake rate from the plateau height and then calculate the PMTT from the integration of the retention function [22].

The calculation of PMTT depends mainly on the first point of the retention function for the matrix inversion deconvolution method and the slope of the straight line for the first phase of the R-P method. We believe that the probability of the error in finding the first point by the first method (which depends on the plateau of the retention function), that can't be easily determined is high, especially for kidneys that function abnormally, whereas the value of the slope which is determined from the straight line (that represents the first phase of the R-P plot), can be accurately and easily determined. So the R-P method may be expected to be more reproducible than the matrix inversion deconvolution method and it can be considered as an alternative technique to find and calculate the renal PMTT.

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