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# Kidney Efficiency Index — quantitative parameter of a dynamic renal scintigraphy. I. Theory and preliminary verification

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## Abstract

**BACKGROUND:** One of the basic clinical indications for dynamic renal scintigraphy (DRS) is a diagnosis of obstructive uropathy and/or nephropathy. Currently, a basic quantitative criterion for diagnosing nephropathy is the percentage of individual kidney's contribution in the global uptake of a radiopharmaceutical from the blood (so-called Split Function - SF). From a clinical point of view, a parameter evaluating a radiopharmaceutical uptake and reflecting the efficiency of a specific kidney, determined independently of the total uptake of both kidneys, would be much more useful. Based on a Rutland theory, a kidney uptake constant K proportional to a radiotracer uptake by individual kidney was introduced and applied to DRS with $^{99m}$Tc-ethylene-1-dicysteine ($^{99m}$Tc-EC). In addition, a kidney efficiency index (KEi) was also worked out as a new parameter obtained by dividing the uptake constant K by the surface of the ROI of a given kidney, which can be interpreted as the average "efficiency" of clearance of a kidney.

**MATERIAL AND METHODS:** K and KEi values were verified in 72 studies selected retrospectively from patients referred routinely for DRS, with available current level of blood creatinine, used for calculation of estimated GFR (eGFR) according to a CKD-EPI formula. After splitting of eGFR values into individual kidneys according to SF, single kidney eGFR values (SKeGFR) were obtained and then used as a verification method for SF, K and KEi values.

**RESULTS:** Correlation between SF and SKeGFR values, $r_{sp} = 0.64$, was significantly weaker ($p < 0.0022$) than the correlation of SKeGFR values with K uptake constants and KEi indices: 0.90 and 0.84, respectively.

**CONCLUSIONS:** Uptake constant K and KEi, as quantitative parameters, give the opportunity to analyze a function of each kidney separately and in an absolute way. KEi also allows for a reliable assessment of kidneys of atypical sizes (larger or smaller than average). It also gives the opportunity to create normative values for this parameter and may be useful in a number of clinical situations where the diagnostic effectiveness of such a relative parameter as SF, is severely limited, e.g. in assessing a large kidney with hydronephrosis or while differing a cirrhotic from hypoplastic (i.e. a small but properly functioning) kidney.

**KEY words:** dynamic renal scintigraphy; renal clearance; split function; uropathy; nephropathy; kidney efficiency index; uptake constant

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## Introduction

In dynamic renal scintigraphy (DRS), imaging of a radiopharmaceutical passage through a patient's kidneys allows the assessment of uptake, transport, and excretion of radiopharmaceutical by these organs. One of the basic clinical indications for DRS is diagnosis of obstructive uropathy and/or nephropathy. Persistent obstructive uropathy (obstruction of the urinary outflow from the calico-pelvic system), manifesting in DRS as a radiopharmaceutical excretion impairment, can lead to damage to the renal parenchyma - obstructive nephropathy, characterized by impairment of radiopharmaceutical uptake and transport function. Currently, a basic quantitative criterion for diagnosing nephropathy is the percentage of individual kidney's contribution in the global uptake of a radiopharmaceutical from the blood [so-called Split Function (SF)]. In a healthy patient, the share of both kidneys in total radiopharmaceutical uptake

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is similar - normal SF values are in the range between 42% and 58% [1, 2].

Although the SF parameter is the basic, routinely used criterion for the diagnosis of nephropathy, it has its significant limitations due to its relative nature. The problem is manifested i.a. in cases of absence or only a trace function of one of kidneys (when the SF of the other kidney will always be close to or equal to 100%, even despite its damage), nephropathy of similar severity affecting both kidneys (both SF values remain in the normal range despite the disease process ongoing in both kidneys) and in case of large differences in the size of kidneys, e.g. hypoplasia of one of them (the share of SF of the smaller kidney will be significantly reduced, despite a normal function of nephrons). From a clinical point of view, a parameter evaluating a radiopharmaceutical uptake and reflecting the efficiency of a given kidney, determined independently of the total uptake of both kidneys, would be much more useful.

In 1984, Rutland [3], taking into account the method of graphic analysis of Patlak [4], presented a comprehensive theory applied to DRS images analysis. In his mathematical model, there was an uptake constant K, which he describes as "a fraction of the blood activity taken up per second". This value was successfully applied to calculate a glomerular filtration rate (GFR) for a single kidney using $^{99m}$Tc-DTPA [5], and in studies using $^{99m}$Tc-MAG3 to determine tubular extraction rate (TER) [6,7]. Despite its potential usefulness, the Rutland method has not gained much popularity and has not yet been applied to a newer radiopharmaceutical — $^{99m}$Tc-ethylene-1-dicysteine ($^{99m}$Tc-EC) [8].

The aim of this study was therefore to present a relatively simple method for generating parameters proportional to the uptake function of a single kidney, independent of the total uptake function of both kidneys. An additional goal was to obtain a parameter independent of kidney size. The parameter should be useful not only in the situations described earlier in which SF is of limited value, but also, for example, in the differentiation between the cirrhotic and hypoplastic kidney (with normal nephron function).

## Material and Methods

### Material

72 patients (47 women, 25 men) aged 17-81 (average 52) years were qualified for the study. They were selected retrospectively from patients routinely referred for DRS, and the entry criterion - qualifying for the study group - was the available current serum creatinine level results in archived medical documentation, which enabled the determination of the approximate glomerular filtration rate eGFR. A total of 138 kidneys were assessed (some patients had only one kidney).

### Study Acquisition

DRS was performed according to a standard procedure. A patient was placed in the supine position with a gamma camera detector (GE Infinia Hawkeye 4) in the posterior projection. Image acquisition was started at the time of intravenous injection of 111 MBq of $^{99m}$Tc-EC. A sequence of 60 images was acquired of 20 seconds each. Counts were stored in a $128 \times 128$ matrix. The camera detector, equipped with a LEHR collimator, was positioned so that its field of view covered — in addition to kidneys — also a heart.

### Preprocessing

Before processing, images were smoothed twice with a typical filter that replaces each pixel with the average of its $3 \times 3$ neighbourhood. An additional image was also created showing the summed counts from the 2 and 3 minutes of the study (parenchymal phase). The images prepared in this way were further processed using the standard and alternative — in house modified method for data processing.

### Regions of interest (ROIs)

To determine areas of kidneys, the image presenting smoothed counts from the 2 and 3 minutes of the study was used. In this image, an isocontour was drawn automatically extracting pixels with values equal to or higher than 30% of the maximum in the image — the ROI generated in this way, if necessary, could be corrected by the operator. ROI areas were also stored for use at a later processing stage. Extra-renal background areas were determined automatically around the lower kidney poles.

Determining a heart ROI — whose size and correct location significantly affect the repeatability of final results — has been automated. An operator used an image showing the first 20 seconds of the study, in which he outlined (with a large margin) the heart area. Twenty pixels with maximum values were automatically searched in the outlined area — and a curve from these pixels (sum of values) was considered a heart curve. Examples of ROIs placement are shown in Figure 1.

### Split Function (SF)

Software available on the Xeleris Functional Imaging Workstation 4.0 (GE Healthcare) dedicated to dynamic renal studies was used for routine study processing. Split Function (SF) was determined from renographic curves after background subtraction, normalized to the areas of respective ROIs. Counts collected during radiotracer
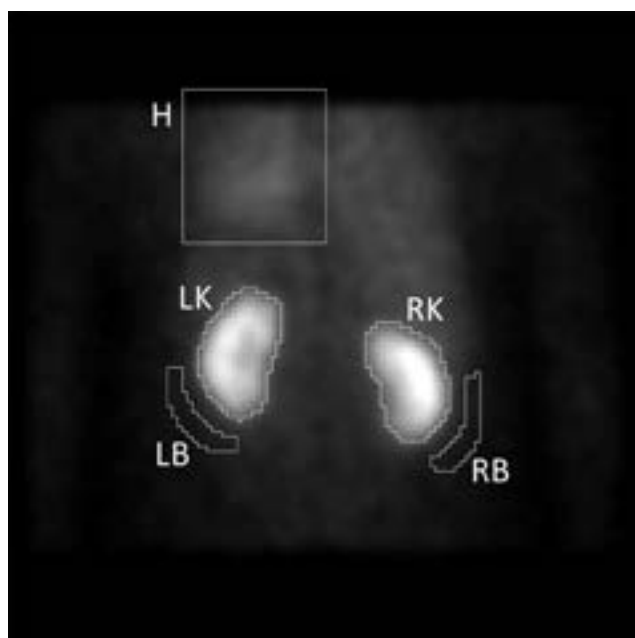


**Figure 1.** Example of heart (H), kidneys (LK, RK), and extrarenal background (LB, RB) ROIs

uptake phase (from 2 to 3 min) were added (integrated) for each curve and then divided by the sum of counts from both kidneys. The result, presented in percent, was the SF value for a given kidney.

### Uptake Constant K

K uptake constants were calculated on the basis of the Rutland method, in which background-corrected kidney and cardiac curves were transformed into so-called Rutland space (Appendix). After transforming the curves, an uptake constant K was determined for each kidney. This value was calculated as an angular coefficient (slope) of line, formed over a time interval between 2 and 3 minutes of the study (from 60 to 160s). According to the theory, the uptake constant value is proportional to clearance function of the individual kidney but has no specific unit. In this paper, phrase "uptake index" was used for description of the graph's axis.

### Kidney Efficiency index

A kidney efficiency index (KEi) is a new parameter obtained by dividing the uptake constant K by the surface of the ROI of a given kidney. This parameter can be interpreted as the average "efficiency" of clearance of a kidney, and it has a unit marked as "uptake index/pixel". Such independence of clearance from a kidney size (in this case from its surface) opens the field for comparing KEi parameters between different kidneys, as well as determining a range of normal values, which should help determine the degree of impairment of kidney function.

### Single Kidney Estimated GFR (SKeGFR)

The reliability of KEi, as an absolute index of renal function, was assessed by comparing its values with the estimated glomerular filtration rate (eGFR) values, which was calculated according to the CKD-EPI formula [9]. This formula takes into account serum creatinine level as well as age, sex, and race of a patient. Serum creatinine levels were obtained from patients' documentation. Testing for serum creatinine level was performed in different labs, but with the same, enzymatic, method. After multiplying eGFR values by the SF percentage values, calculated earlier for each kidney, a parameter determining estimated eGFR value for individual kidneys (Single Kidney estimated GFR — SKeGFR) was obtained. Unit for the SKeGFR was the same as eGFR unit,
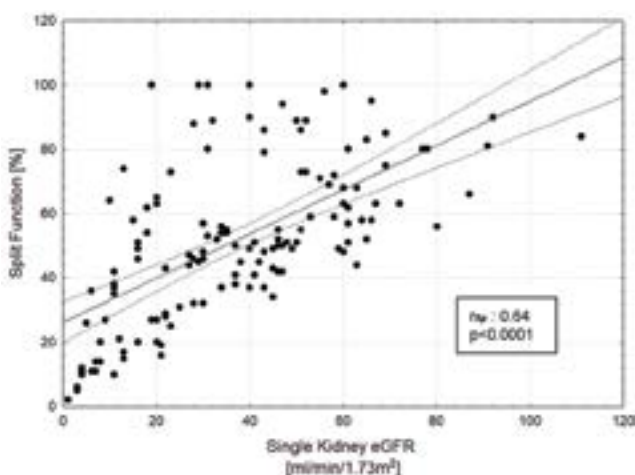


**Figure 2.** Scatter plot of Split Function (SF) and SKeGFR ($r_{Sp} = 0.64$) with regression line and its 95% confidence interval
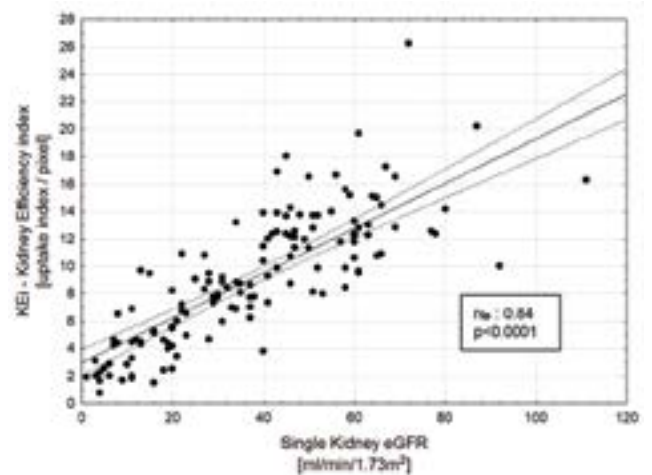


**Figure 4.** Scatter plot of KEi and SKeGFR ($r_{Sp} = 0.84$) with regression line and its 95% confidence interval
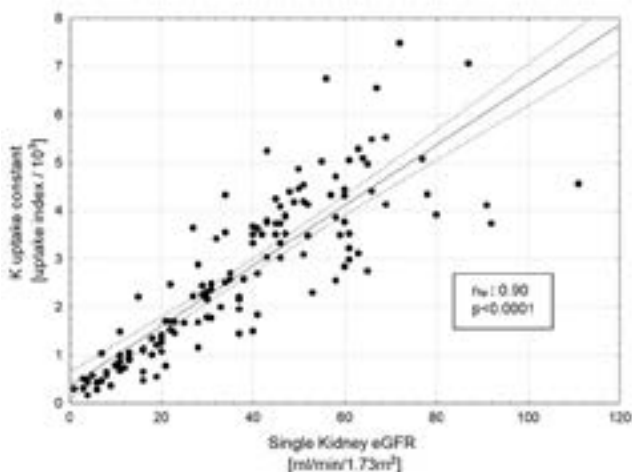


**Figure 3.** Scatter plot of uptake constant K and SKeGFR ($r_{Sp} = 0.90$) with regression line and its 95% confidence interval
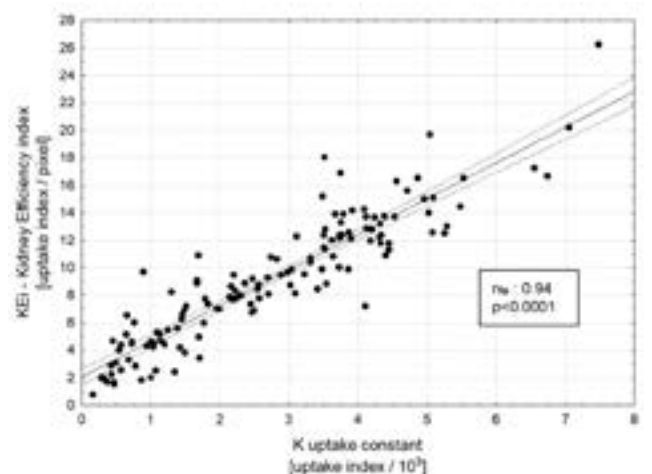


**Figure 5.** Scatter plot of KEi and K uptake constant ($r_{Sp} = 0.94$) with regression line and its 95% confidence interval
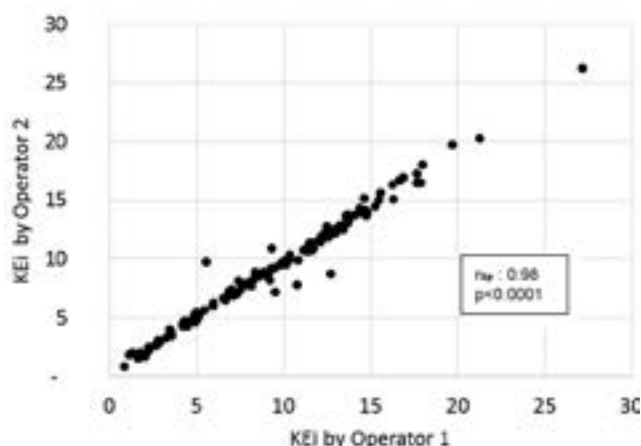
**Figure 6.** KEi values: Operator 1 and Operator 2

which is [mL/min/1.73 m²]. SKeGFR values were compared with previously obtained SF parameters and K uptake constants.

### Inter-observer variability

All activities related to the study results were carried out twice, by different operators. Before processing, both operators underwent training unifying their proceedings, in particular how to determine ROIs. Values obtained by both operators were compared in order to assess the repeatability of study results.

## Statistical analysis

The least squares method was used to approximate straight lines. Spearman's coefficients ($r_{sp}$) examined correlations between the SF and SKeGFR parameters, between the uptake constant K and SKeGFR, and between KEi parameters calculated by both operators.

## Results

The correlation between SF and SKeGFR values turned out to be statistically significant $r_{sp} = 0.64$ (p < 0.0001, Fig. 2), but this relationship was significantly weaker (p < 0.0022) than the correlation of SKeGFR values with K uptake constants and KEi indices: 0.90 and 0.84, respectively (p < 0.0001). Figures 3 and 4 present scatter plots of these values. Correlation between K uptake constants and KEi values (Fig. 5) was very high and statistically significant $r_{Sp} = 0.94$ (p < 0.0001). The repeatability of the KEi parameter determination by various operators turned out to be very high $r_{Sp} = 0.986$ (Fig. 6).

## Discussion

Gamma camera methods determining clearance function separately for each kidney were introduced in the seventies of the twentieth century [10, 11], and in the eighties and nineties, a methodology of these studies was improved [5, 12, 13]. The method for clearance calculation was based on a relationship between a radiotracer uptake by a kidney (in per cent) and its concentration in blood plasma. Based on proportionality coefficients between

these values, the clearance functions of both kidneys were estimated separately. Initially, this method was used to determine only a glomerular filtration rate — GFR [10, 11], because 99mTc-DTPA was the only radiopharmaceutical labelled with radiotechnetium available at that time. At the beginning of the nineties, a similar methodology was used to estimate clearance of a newly introduced radiopharmaceutical — 99mTc-MAG3, secreted in renal tubules [7, 13]. For normalization purposes, however, these methods required measurement of a patient's blood sample as well as consideration of a camera sensitivity while converting counts into activity. This was done by measuring by gamma camera a syringe with a radiopharmaceutical prepared for administration and a residual of activity in the syringe after injection. In addition, the need to apply corrections for extra-renal background, radiation absorption dependent on the kidney depth, radiation absorption by a couch and normalization of clearance values to patient body surface were emphasized. In subsequent versions of the methodology, the blood sample was no longer necessary. Clearance, expressed as a percentage of uptake of administered activity by kidneys, was then converted to clearance-specific units by using appropriate nomograms [14]. However, none of these methods has been used so far for the radiopharmaceutical 99mTc-ethylenedicysteine (99mTc-EC) [8].

The Rutland method used in this work [3] is based on the determination of a regression line between two quantities that change during the first 3 minutes after administration of a radiotracer, that is, before it begins to leave a kidney.

This applies, on one side of the equation, to the ratio of radiopharmaceutical uptake in a kidney, normalized to its level in the blood (approximated by a curve from the heart as a large reservoir of blood) and on the other side of the equation, to the total (integrated) flow of the radiopharmaceutical through the heart, also related to its level in blood (Appendix). In the classic Rutland method, a slope of a straight line of regression referred to as the "uptake index" [5], is proportional to the radiotracer clearance of a given kidney. It is assumed in this method, that the intravascular part of the extra-renal background changes proportionally to the curve determined from above the heart as the largest blood reservoir.

Peters [15] believes that this method has the smallest statistical error among other gamma camera methods used for clearance calculation. However, despite the fact that the possibility of using this method to determine the clearance of 99mTc-DTPA of each kidney was presented as early as in 1985, it did not find application, with a few exceptions [7, 16], in later works — probably due to its relatively high mathematical complexity [17]. However, it has been mentioned in the literature, mainly in the context of calculating split function [1, 18], although it was not adopted in this application either [19]. Instead, it was successfully used to generate parametric images of the kidneys [20–22].

Advantages of this method used to separately assess the function of each kidney, are significant. It is a simplified version of a gamma camera clearance measurement based only on the automated determination of areas of kidneys, heart, and the extra-vascular background. The fact that this method does not require normalization of calculated values to administered activity facilitates its application. Disregarding administered activity causes that parameters determining the efficiency of each kidney (K uptake constant and KEi index) are unnamed quantities proportional to their clearance function [5].

In case of the KEi parameter, dividing K uptake value by the surface of the kidney (its ROI) made the value independent of kidney size. Such a quantitative parameter not only gives the opportunity to analyze a function of each kidney separately and in an absolute way, but also allows for reliable assessment of kidneys of atypical sizes (larger or smaller than average). It also gives the opportunity to create normative values for this parameter. KEi may be useful in a number of clinical situations where the diagnostic effectiveness of basic parameters of dynamic renal scintigraphy, such as SF, is severely limited. Its absolute nature allows reliable differential diagnosis of uropathy and obstructive nephropathy in case of a single kidney or bilateral renal impairment. Its independence from kidney size will be important, e.g. in assessing a large kidney with hydronephrosis. Due to the greater initial amount of parenchyma of such a kidney, SF can remain within the normal range despite damage to some of its nephrons, while KEi will decrease already in the initial phase of obstructive nephropathy. A similar problem is met while differing a cirrhotic from hypoplastic (i.e. a small but properly functioning) kidney, where SF will be below the normal limit in both cases, while KEi will be lowered only in the kidney damaged.

The comparison of the K uptake constant (reflecting the clearance of individual kidney) and the KEi index with estimated GFR values (calculated on the basis of creatinine level, each time converted to individual kidney in accordance with its relative contribution to radiopharmaceutical uptake) was used in this paper as a verification of these parameters' usefulness in the assessment of renal function.

The two presented parameters, K uptake constant and KEi index (Fig. 5), correlate highly with each other (0.94) but their meanings are slightly different. According to Rutland theory, K uptake constant corresponds strictly to kidney clearance, which is dependent on kidney size, and this is why the correlation coefficient between K and SKeGFR has the highest value (0.90). KEi parameter, because of its average nature, corresponds more to kidney efficiency and is independent of kidney size. For this reason, correlation coefficient between KEi and SKeGFR is lower (0.84), but KEi still correlates strongly with kidney clearance.

A greater spread of the K uptake constant around a regression line in patients with higher eGFR levels (Fig. 3) is caused by errors of eGFR values at such levels [9], i.e. due to the imperfections of the verification method. Another source of the scatter on the graphs (Fig. 3, 4) might be the fact that testing for serum creatinine level was performed in different labs, using tests from different producers. However, higher correlation coefficients between the K and SKeGFR uptake constant and KEi and SKeGFR than between SF and SKeGFR (0.90 and 0.84 vs 0.64) indicate higher usefulness of those parameters in assessment of uptake function of individual kidneys by these values than SF.

Due to the retrospective character of this preliminary analysis, it was impossible to use more accurate, measured GFR (e.g. using $^{99m}$Tc-DTPA clearance) as a reference method. This will be the subject of a future prospective study.

The presented method ensures high repeatability mainly due to the high automation of data processing. The most important was a reproducibility of a method generating a heart curve. Using an average value of the highest 20 pixels within heart ROI means that shape and area under a cardiac curve remained the same regardless of an operator processing the study. In case of

renal curves, an isocontour method (30% of the maximum value in the kidney) applied to summed images of second and third minutes of the study was of great importance. However, in cases when fragments of renal parenchyma were omitted by isocontour or when kidney shape was atypical — it was necessary to manually draw a fragment or the entire kidney ROI.

The method also avoids errors introduced by the need to measure the administered activity. Thanks to this, even a paravenous injection should not affect negatively the quantitative parameters of kidney function.

Our method also assumes, as demonstrated by Rehling et al. [5], that the absorption of radiation emitted by kidneys is similar to the absorption of radiation coming from the heart (these effects cancel each other out), hence it is not necessary to apply corrections accounting for the absorption of radiation. As Rehling et al. showed, these corrections can be omitted, especially in the light of the fact that differences in the depth of the kidneys in patient in the lying position, exceeding 1 cm, are relatively rare [23].

## Conclusions

A method of calculating the uptake constant K (value proportional to kidney clearance) presented here in application to $^{99m}$Tc-EC, due to its high degree of automation, is characterized by high repeatability. In clinical situations where the classic parameters of dynamic renal scintigraphy are unreliable, the use of the KEi parameter (average clearance per pixel) should improve the diagnostic effectiveness of this study, including differential diagnosis of uropathy and obstructive nephropathy or cirrhotic and hypoplastic kidney.

## Appendix

Rutland space — a space described by variables created on renographic and cardiac curves. At the initial stage of the renoscintigraphic examination (2–3 minutes of the study), the distribution of points in this space is approximated by a straight line described by the equation:

$$\frac{R(t)}{H(t)} = K \cdot \frac{\int_0^t H(t)dt}{H(t)} + F \qquad (E1)$$

where:

R(t) — kidney (renographic) curve after background subtraction

H(t) — cardiac curve. The author's modification of the method uses of a sum of 20 pixels with maximum values within the heart ROI,

F — blood background subtraction factor,

K — uptake constant, fraction of blood activity taken up per time unit — can be calculated as a slope of the straight line described by equation E1. This value reflects the clearance of individual kidneys and is dependent on kidney size. After dividing this value by kidney ROI area, the KEi parameter was obtained, reflecting the average efficiency of the kidney in filtering blood.

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