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Application of normalized values of kidney clearance function in the diagnosis of bilateral obstructive nephropathy — a preliminary report

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Abstract

BACKGROUND: Dynamic renal scintigraphy provides effective diagnosis of obstructive uropathy and nephropathy. However, in case of a bilateral outflow impairment, relative differential renal function (DRF), which is a primary quantitative criterion for diagnosis of unilateral obstructive nephropathy (when its value is below 45%, according to EANM guidelines from 2011), becomes unreliable. In case of bilateral nephropathy with similar severity, this parameter may even be within the normal range (45–55%) for both kidneys. The aim of this study was therefore to assess diagnostic usefulness of the original, normalized, absolute parameter proportional to the value of renal clearance function (K) in the evaluation of obstructive nephropathy in a group of patients with bilateral uropathy.
MATERIAL AND METHODS: 16 healthy volunteers (32 kidneys) without history of kidney diseases were examined to determine normative value of K index. Then, 8 patients (16 kidneys) with bilateral obstructive uropathy found in standard dynamic renal scintigraphy performed using 111 MBq of 99mTc-EC (cumulative renographic curve that continued rising or dropped by less than 50% after i.v. administration of Furosemide) were examined. For each of the subjects 60 sequential 20s images were obtained, which were then assessed using an original method of post-processing scintigraphic data. It included normalization of renographic curves to the area under the heart curve. Subsequently, these normalized values from the uptake phase (between 2nd and 3rd minute) were inserted into the linear regression equation, from which K index was obtained.
RESULTS: In healthy volunteers the average value of K index was 0.23 ± 0.05. The value of 0.13 (mean –2 SD) was taken as the lower limit of the norm. Values below that limit suggest obstructive nephropathy. In patients with bilateral obstructive uropathy, 5 kidneys met the conventional criteria of nephropathy (DRF < 45%), while 11 kidneys had DRF within normal range. K index was below the norm in 9 kidneys (including 4 kidneys with low and 5 with normal DRF), while its value was normal in 7, including one kidney with reduced DRF (37%). K index changed the diagnosis in 6 kidneys out of 16 (38%).
CONCLUSIONS: Preliminary results indicate usefulness of K index in diagnosis of obstructive nephropathy in patients with bilateral obstructive uropathy. For further evaluation of clinical value of this method, it is planned to examine a larger group of patients with varying degrees of renal parenchymal function impairments.

KEY words: hydronephrosis; radioisotope renography; radiopharmaceuticals; technetium Tc 99m-ethylenedicysteine

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Introduction

One of the main applications of dynamic renal scintigraphy (DRS) is the diagnosis of obstructive uropathy and nephropathy [1].

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The basic quantitative criterion for the diagnosis of unilateral obstructive nephropathy is the relative, differential function of each kidney in the global uptake (differential renal function — DRF) [2, 3]. In some situations, however, this parameter may be unreliable. Among other things, in case of bilateral nephropathy with a similar degree of severity on each side, the value of this parameter may be within the normal range (45–55%). In studies where only posterior projections were obtained (eg. with a single-head gamma camera), it may also be affected by a different depth of each kidney, and thus differing absorption of radiation by tissues located between the kidney and the detector, or as shown by Wehbi et al., by significant hydronephrosis [4]. In addition, DRF does not apply to the evaluation of the uptake function of a single kidney (eg. after a nephrectomy or in case of no or minimal amount of functioning parenchyma of the second kidney), since it will always be close to 100%, even if the function of its parenchyma is impaired. An objective, quantitative assessment of renal parenchymal function based on DRS is practically impossible in the above-mentioned situations. All that remains is a subjective, visual assessment of scintigraphic images (eg. increased background activity) or prolonged transit time of the radiopharmaceutical (RF) through renal parenchyma (parenchymal transit time — PTT) [5]. However, PTT calculation is not commonly performed and may be difficult in case of significant retention of RF in the expanded pelvicalyceal system (PCS).

Aim

The aim of the study was to develop a normalized parameter proportional to the absolute value of the renal clearance function (K), determine its normative values and assess its usefulness in the diagnosis of obstructive nephropathy in a group of patients with bilateral obstructive uropathy.

Material and methods

The control group used to determine the normative values of K index consisted of 13 healthy volunteers and 3 healthy kidney donor candidates (in total, values of this parameter were calculated for 32 kidneys). The criterion of inclusion in this group was the absence of kidney diseases (in history), diabetes, hypertension, or other diseases, including systemic ones, which may impair the function of these organs. The results of current laboratory tests (urea and creatinine levels, urinalysis) were within normal ranges. Also in ultrasonography of the urinary system carried out on the day of the scintigraphic examination, no signs of urolithiasis, dilatation of PCS or other pathologies were found.

In each of the subjects, after previous hydration (500 ml of water about 30min before the examination) and emptying of the bladder, DRS was performed using gamma cameras: Infinia Hawkeye, Infinia Hawkeye 4 or Optima NM/CT 640 equipped with low-energy, general purpose (LEGP) collimators with 111 MBq 99Tc-EC as radiopharmaceutical (RPh). 60 twenty-second images in a 128 x 128 matrix in a posterior projection, with both kidneys and heart within the field of view, were obtained (images in anterior projection were also obtained, for use in further studies).

Each of the images was then processed using the original plugin for the open source image processing program ImageJ, that was developed in our department. After smoothing the images twice, the areas of interest for kidneys and heart were determined. On the first 20-second image, a rectangular ROI was drawn in an area of the heart (ROI-H), and on the image of the uptake phase (2nd summed one-minute image) kidney ROIs (ROI-K) were drawn using a semi-automatic method (with a manually selected threshold).

Then on each of 60 images, the program automatically selected 20 pixels with the largest number of counts in the ROI-H. A temporary cardiac curve (H_0) was obtained in this way and was used as a basis for image standardization. Each pixel on each of the 60 images was divided by the integral of H_0, i.e. by the area under the temporary cardiac curve. Next, from images standardized in this way, renal curves (as mean values of counts per pixel in ROI-N), as well as the proper heart curve (as an average of counts in 20 pixels with maximum values in ROI-H) were obtained.

Values from the uptake phase (from 4th to 8th image, i.e. from 60th to the 160th second of the study) were selected for further analysis. In accordance with Rutland's theory, a normalized K index was determined for each kidney in a group of healthy volunteers and its normative values were calculated.

Then, eight patients (16 kidneys) were selected from the patients indicated for DRS in our department in 2017–2018, in whom scintigraphy (also performed according to the standard protocol described above) revealed a retention of RPh (cumulative renographic curves), that after i.v. administration of the diuretic (0.5 mg/kg of Furosemide) at the 20th minute persisted or decreased by less than 50%, which is a scintigraphic criterion for the diagnosis of obstructive uropathy. RPh uptake in the renal parenchyma was assessed visually and evaluated on a three-point scale: (-) — homogeneous, normal RF uptake in the kidney parenchyma, (M) — mild cortical defect(s), (S) — severe cortical defect(s). Then, the K index was determined for each of the examined kidneys by means of post-processing of scintigraphic data. Obtained results were compared with the previously calculated normative values.

Results

In the control group, the mean value of the K index was 0.23 ± 0.05. The value of 0.13 (average $-2 \times$ SD) was taken as the lower limit of the norm, assuming that lower values suggest the impairment of renal parenchymal function, i.e. obstructive nephropathy.

The values of the K index in the group of patients with bilateral obstructive uropathy (n = 16 kidneys) are summarized in Table 1. In this group, 5 kidneys met the conventional criterion of obstructive nephropathy (DRF < 45%), while DRF of 11 was within the normal range. The K index was below the norm in 9 kidneys (including 4 kidneys with lowered and 5 with normal DRF), while its value was within normal range for the remaining 7 kidneys, including one kidney with reduced DRF (where K reached 0.14 with DRF = 37%). The diagnoses based on DRF and K index were consistent in 10 cases, while in 6 kidneys (38%) were incompatible, as shown in Figure 1.

Discussion

There are clinical situations where the diagnostic value of DRF obtained from DRS is significantly reduced. One of them is an impairment of the parenchymal function of both kidneys of similar severity. Visual evaluation of scintigraphic images can be helpful only in the assessment of extensive deficiencies in the renal parenchyma (areas of reduced uptake) or kidney failure (increased activity in the background). The quantitative analysis with the calculation of PTT, using the deconvolution technique, also has limitations [6]. Determination of the renal parenchyma ROI, necessary to obtain the value of this parameter, can be difficult, especially in the case of dilated pelvicalyceal system and a significant compression of the parenchyma. The technique of deconvolution itself requires specialized

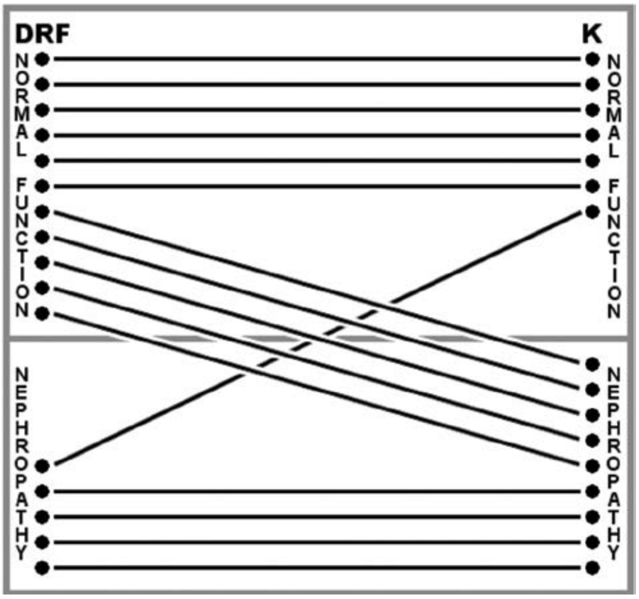

Figure 1. Compatibility of nephropathy diagnoses based on DRF vs K index

software that is not included in the standard workstations available with gamma cameras and can also generate errors.

Combining DRS with the multi-sample, radioisotope clearance technique of determining GFR [7] allows the assessment of the function of each kidney separately. However, this is a labour-intensive and time-consuming method, and it is not routinely used in nuclear medicine departments. Estimated GFR (eGFR) calculated from serum creatinine levels and even GFR determined from the creatinine clearance in a 24-hour urine collection, can confirm only severe renal function impairments with already developing renal failure. Other medical imaging techniques do not enable the diagnosis of nephropathy with a relatively low severity either.

Therefore, the reliability of diagnoses obtained from the assessment of the K index was evaluated based on theoretical premises of the method. The formula used to obtain its value was derived based on the established Rutland's theory [8]. According to this theory, kidney function can be described by the equation, where R(t) — counts inside ROI-N changing with time (renal curve), P(t) — blood radiotracer concentration (obtained from the heart curve), F — free expression, Q(t) — cumulative radiotracer activity that flowed through the heart from the time of administration of the radiopharmaceutical to the time t, K — parameter proportional to the kidney clearance function. Since this is a linear function formula, K coefficient, as the slope of the function, has been determined using linear regression with the least squares method. So far such determination of renal clearance function has been used only to obtain clearance parametric images, which have displayed high effectiveness in the diagnosis of focal lesions in these organs (scars, lesions after ESWL) [9,10].

These premises clearly indicate a close relation between the values of K index and the renal clearance function. In addition, due to the fact that the curves are normalized to the number of counts in the heart area, obtained values of K index do not depend on such factors as e.g. the activity of RPh administered to the patient. Considering the above, it is possible to compare values of K index obtained in repeat tests performed in a patient, as well as to compare its values in different patients.

In all kidneys that met the standard criteria for the diagnosis of obstructive nephropathy (DRF $<$ 45%), only in one case the K index was close to the lower limit of the norm, although within its normal range (0.14 for a kidney with DRF of 37%). However, the K index allowed to additionally find indications of nephropathy in 5 kidneys with normal DRF.

Confirmation of the clinical usefulness of the developed method requires examining more patients, with both bilateral and unilateral renal function impairments, but the initial results obtained so far give basis to assume that it can be widely used in scintigraphic diagnostics, not only of obstructive nephropathy but also kidney function impairments from other causes.

Conclusions

Preliminary results show the usefulness of the developed K index in the diagnosis of obstructive nephropathy in patients with bilateral outflow impairments. It should be assumed that the determination of this parameter will significantly increase the diagnostic value of dynamic kidney scintigraphy. In order to further evaluate its potential clinical applications, it is planned to examine a larger number of patients with varying degrees of renal parenchymal function impairments.

Table 1. Comparison of values of the K index with standard scintigraphic parameters in the group of patients with bilateral obstructive uropathy

	Left kidney			Right kidney		
Patient n = 8	Visual assessment[1]	DRF [%] N ≥ 45	K N ≥ 0.13	Visual assessment[1]	DRF [%] N ≥ 45	K N ≥ 0.13
1	M	45	0,14	-	55	0,12
2	S	42	0,08	M	58	0,11
3	-	50	0,28	-	50	0,29
4	-	47	0,12	-	53	0,13
5	-	62	0,1	M	38	0,09
6	M	73	0,09	S	27	0,03
7	-	63	0,28	M	37	0,14
8	S	5	0,03	-	95	0,13

[1]Visual assessment: (-) — homogeneous, normal RPh uptake in renal parenchyma; (M) — mild cortical defect(s); (S) — severe cortical defect(s)

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