Eur J Nucl Med Mol Imaging (2009) 36:1665–1673
DOI 10.1007/s00259-009-1138-5

ORIGINAL ARTICLE

Diuretic renography in hydronephrosis: renal tissue tracer transit predicts functional course and thereby need for surgery

Andreas Schlotmann · John H. Clorius · Sandra N. Clorius

Received: 9 November 2008 / Accepted: 26 March 2009 / Published online: 13 May 2009

Abstract
Purpose The recognition of those hydronephrotic kidneys which require therapy to preserve renal function remains difficult. We retrospectively compared the 'tissue tracer transit' (TTT) of ^{99m}Tc-mercaptoacetyltriglycine (^{99m}Tc-MAG_3) with 'response to furosemide stimulation' (RFS) and with 'single kidney function<40%' (SKF<40%) to predict functional course and thereby need for surgery.
Methods Fifty patients with suspected unilateral obstruction and normal contralateral kidney had 115 paired (baseline/follow-up) ^{99m}Tc-MAG_3 scintirenographies. Three predictions of the functional development were derived from each baseline examination: the first based on TTT (visually assessed), the second on RFS and the third on SKF<40%. Each prediction also considered whether the patient had surgery. Possible predictions were 'better', 'worse' or 'stable' function. A comparison of SKF at baseline and follow-up verified the predictions.
Results The frequency of correct predictions for functional improvement following surgery was 8 of 10 kidneys with delayed TTT, 9 of 22 kidneys with obstructive RFS and 9 of 21 kidneys with SKF<40%; for functional deterioration without surgery it was 2 of 3 kidneys with delayed TTT, 3 of 20 kidneys with obstructive RFS and 3 of 23 kidneys with SKF<40%. Without surgery 67 of 70 kidneys with timely TTT maintained function. Without surgery 0 of 9 kidneys with timely TTT but obstructive RFS and only 1 of 16 kidneys with timely TTT but SKF<40% lost function.
Conclusion Delayed TTT appears to identify the need for therapy to preserve function of hydronephrotic kidneys, while timely TTT may exclude risk even in the presence of an obstructive RFS or SKF<40%.

Keywords Glomerular filtration rate · Radioisotope renography · Renin-angiotensin system · Ureteral obstruction

Introduction

It remains unclear which patients with obstructive renal disease benefit from surgery [1–4]. Among other tests captopril and diuretic renography deliver important parameters to determine the need for surgical intervention, but none of the commonly used parameters based on these tests accurately predict functional deterioration [1, 2, 5–8]. In an animal experimental study it was recently shown that delayed 'tissue tracer transit' (TTT) of ^{99m}Tc-mercaptoacetyltriglycine (^{99m}Tc-MAG_3), a parameter derived from renography, accompanies both functional decline and histomorphological restructuring of hydronephrotic kidneys [9]. In a retrospective clinical study the parameter TTT was now compared with the commonly used parameters 'response to furosemide stimulation' (RFS) and 'single kidney function<40%' (SKF<40%) to predict the functional development and thereby the need for surgery of hydronephrotic kidneys.

An editorial commentary on this paper is available at http://dx.doi.org/10.1007/s00259-009-1160-7.

A. Schlotmann (✉)
Department of Nuclear Medicine and Department of Radiation Oncology, University Hospital Freiburg, Hugstetter Str. 55, 79106 Freiburg, Germany
e-mail: Andreas.Schlotmann@Uniklinik-Freiburg.de

J. H. Clorius
German Cancer Research Center, Heidelberg, Germany

S. N. Clorius
Department of Internal Medicine, University Hospital Basel, Basel, Switzerland

Materials and methods

Patients were included in the 4-year study when radiologic or ultrasound examinations suggested unilateral obstruction. The exact diagnosis was usually unknown. The contralateral kidney had to be without recognizable abnormality. Fifty patients (37 male, 13 female) between 1 week and 86 years of age (median: 2 years) had a total of 169 ^{99m}Tc-MAG$_3$ diuretic gamma camera renograms. The paediatric population (up to 13 years, median: 1 year) consisted of 37 children and the adult population (older than 22 years, median: 40 years) of 13 patients. Well-hydrated patients had supine position renography. Adults received 0.37 MBq ^{99m}Tc-MAG$_3$/kg body weight and children 2.59 MBq ^{99m}Tc-MAG$_3$/kg body weight. Data from the first 18 months are based on the F+10 protocol and afterwards on the F+20 as recommended in the Consensus Report on Diuresis Renography [10]. The dosage of furosemide was 0.5 mg/kg (maximum 40 mg) in adults and 1.0 mg/kg (maximum 20 mg) in children, respectively. The examinations were obtained with a large field of view camera (Siemens e.cam) with a low-energy, all-purpose collimator. The duration of the study was 20 min: 5 s/frame for 3 min, 10 s/frame for 7 min and 30 s/frame for 10 min. One minute scintiscans were made from the first through the fifth minute and at 8, 10, 15, 19 and 20 min. If furosemide was given after 20 min, an additional 20-min acquisition followed. A final 1-min scintiscan was always obtained after micturition. The camera setting was not changed prior to the post-micturition image.

Two experienced nuclear medicine specialists blinded to clinical data were presented the 169 renograms at irregular intervals in random order. Both reviewers evaluated two parameters derived from each examination: TTT, which was assessed visually, and RFS.

TTT of ^{99m}Tc-MAG$_3$ was classified as timely, delayed or indeterminate based on visual assessment. Timely TTT was defined as a physiological transit of the tracer through the parenchyma into the pelvis, and delayed as an unphysiological, and clearly slowed transport. TTT was considered indeterminate when it was impossible to arrive at a definite classification. The primary goal was to determine whether the tracer is retained in the renal parenchyma or transported in a timely manner from the parenchyma into the pelvis. The following criteria identify delayed TTT: (1) The pelvis is visualized as being photopaenic between the 2nd and 6th/8th min. (2) A relatively stable tracer distribution within the kidney over time. Thus shape and size of the kidney remain nearly unchanged from the 2nd/3rd min to the 8th/10th min, or beyond. (3) Activity in the parenchyma increases with time, or does not decrease adequately after the 2nd/3rd min. (4) Clearance of tracer out of the parenchyma into the pelvis is delayed, determined by comparing the hydronephrotic kidney with the contralateral healthy organ, i.e. the obstructed kidney appears enlarged in late images due to tracer retention in the periphery of the parenchyma, or later appearance of tracer in the pelvis of the obstructed kidney, compared to the non-obstructed kidney.

RFS was classified as non-obstructive, obstructive and equivocal [11]. Renograms which required no furosemide and those with prompt washout after furosemide were classified as non-obstructive. Kidneys with an empty pelvis on the post-micturition image were also classified as non-obstructive. The pre- and post-micturition images were visually evaluated together. The renogram curves were evaluated quantitatively. An obstructive RFS was defined as no decline after furosemide or a convex descent of less than 50% from maximum. An equivocal result was noted when it was not possible to classify a result with certainty.

SKF was determined with the region of interest (ROI) technique and background-subtracted time activity curves. The kidney ROIs were placed by the technician along the outer rim of both kidneys (whole kidney ROI: cortex, calyces and pelvis). The background ROI was located midline, slightly above the renal pelvis. SKF was determined with a commercial program (e.cam, Siemens) using the area under the curve method.

Each examination served as baseline study when a follow-up existed. The baseline examination provided baseline SKF and three independent predictions of the functional development. The first prediction was based on TTT (visually assessed), the second on RFS and the third on SKF<40%. (Note that baseline SKF documented the obstructed kidneys' relative function, while SKF<40% is one of the three parameters which were used to predict future function.) Each prediction also considered the treatment course, i.e. whether or not surgery had occurred between baseline and follow-up. The accuracy of these three predictions was separately evaluated to compare the predictive power of TTT (Table 3) with the predictive power of RFS (Table 4) and with the predictive power of SKF<40% (Table 5). Possible predictions were 'better' (functional improvement expected), 'worse' (functional decline expected) or 'stable' (no change in function expected).

The algorithms used to predict the functional development are demonstrated in Tables 3–5, columns 3–5. If patients had surgery and the parameter used for the prediction was 'not normal', then delayed TTT (group 1A), obstructive RFS (group 2A) and SKF<40% (group 3A) led to the prediction that function would improve ('better'). If surgery was withheld, functional decline ('worse') was predicted for delayed TTT (group 1B), obstructive RFS (group 2B) and SKF<40% (group 3B). If patients were referred to surgery and the parameter was 'normal', then timely TTT (group 1C), non-obstructive RFS (group 2C) and SKF>40% (group 3C) led to the prognosis of stable function. If surgery was withheld, a stable function ('stable') was also predicted for

timely TTT (group 1D), non-obstructive RFS (group 2D) and SKF>40% (group 3D). The comparison between the baseline SKF and the immediate follow-up SKF verified each of the three predictions. An absolute change in SKF >5% was considered significant [12]. Thus, the functional prediction 'better' was considered correct in case of an improvement of SKF >5%, the prediction 'worse' in case of a decline >5% and 'stable' in case of a functional change≤ 5%. The healthy contralateral kidney was considered to have stable function.

Because one examination could serve as baseline, and as follow-up, the 169 renograms were finally evaluated as 115 paired studies. For example, if one patient had four renograms, the first and the second, the second and the third and the third and the fourth were paired, each pair having a baseline and follow-up. Accordingly four examinations resulted in three paired studies.

In 27 of the 169 examinations the reviewers differed on TTT. A consensus discussion obtained a single response. Clearly divergent results (timely vs delayed TTT) were only observed 3 times, and 24 times one reviewer arrived at a definitive result (timely or delayed TTT), while the other expressed uncertainty (indeterminate TTT).

There were instances where one reviewer classified the RFS as equivocal and the other as obstructive or non-obstructive. The equivocal response was dropped, and the secure diagnosis (non-obstructive or obstructive RFS) was used for the classification.

In one paired study the kidney had delayed TTT and an obstructive RFS prior to surgery. For both parameters the resulting prediction was 'better'. But the kidney was not expected to show further improvement because SKF before surgery was 50%. Therefore this paired study was excluded from the evaluation of the predictions.

The average time between two paired examinations was 240±177 days. All results are presented as mean values± standard deviation.

Results

A total of 115 paired studies were evaluated. All kidneys (14) with delayed TTT showed an obstructive RFS (Table 1). This was fundamentally different in the 85 kidneys with timely TTT, which included 15 kidneys with an obstructive, 36 with an equivocal and 34 with a non-obstructive RFS. SKF<40% was seen in 12 of 14 kidneys with delayed TTT, in 10 of 16 with indeterminate TTT and in 22 of 85 with timely TTT (Table 2).

Maturation of the kidney, in terms of ^{99m}Tc-MAG$_3$ clearance, is complete at the end of the 1st year of life [13]. In the text that follows, the number of correct predictions are presented separately for infants in their 1st year of life and for older patients.

Parameter TTT (Table 3)

Thirteen kidneys were considered at risk due to a delayed TTT:

- As a consequence ten had surgery. Our model predicted functional improvement (Fig. 1). In eight the function of the hydronephrotic kidney improved after surgery (+20±8%), while two remained unchanged (+2±1%), leading to eight correct predictions (infants: three of four; non-infants: five of six).
- Nevertheless, three had no surgery. Reduced SKF (−27±23%) was correctly predicted for two (no infants; non-infants: two of three) and one remained stable (+2%).

Eighty-five kidneys were not considered at risk due to a timely TTT:

- In spite of this 15 had surgery. Stable function (±0±3%) was correctly predicted in 11 (infants: 1 of 2; non-

Table 1 ^{99m}Tc-MAG$_3$ diuretic scintigraphy of 115 kidneys with suspected obstruction

Tissue tracer transit	Total			Response to furosemide stimulation								
				Obstructive			Equivocal			Non-obstructive		
	Total	Surgery	No surgery	Total	Surgery	No surgery	Total	Surgery	No surgery	Total	Surgery	No surgery
Delayed	14	11	3	14	11	3	0	0	0	0	0	0
Indeterminate	16	7	9	14	6	8	2	1	1	0	0	0
Timely	85	15	70	15	6	9	36	4	32	34	5	29
Total	115	33	82	43	23	20	38	5	33	34	5	29

The comparison of TTT and RFS shows that kidneys with an obstructive RFS can have a delayed or a timely TTT while kidneys with delayed TTT always have an obstructive RFS

Table 2 ^{99m}Tc-MAG$_3$ diuretic scintigraphy of 115 kidneys with suspected obstruction

Tissue tracer transit	Total			Single kidney function					
				<40%			≥40%		
	Total	Surgery	No surgery	Total	Surgery	No surgery	Total	Surgery	No surgery
Delayed	14	11	3	12	10	2	2	1	1
Indeterminate	16	7	9	10	5	5	6	2	4
Timely	85	15	70	22	6	16	63	9	54
Total	115	33	82	44	21	23	71	12	59

Comparison of TTT and SKF <40%

infants: 10 of 13), while it declined unexpectedly in 4 (−18±10%).

- Seventy had no surgery. Predicted stable function (±0±3%) was verified in 63 (infants: 34 of 38; non-infants: 29 of 32). Surprisingly function improved in four (+8±2%) and declined in three (−25±21%). Of these 70 kidneys, 9 had an obstructive RFS, and all 9 remained functionally stable (+1±2%); 16 of these 70 kidneys had a SKF<40%. Of these 16 kidneys, 12 remained stable (−1±3%), 3 improved (+8±2%) and 1 declined (−8%).

TTT was indeterminate in 16 studies, mostly due to the inability to differentiate parenchymal from pelvic activity.

Parameter RFS (Table 4)

Forty-two kidneys were considered at risk due to an obstructive RFS:

- As a consequence 22 had surgery and improvement was predicted. SKF improved in 9 (+18±9%), 11 were unchanged (−1±4%) and 2 declined (−24±12%). Nine predictions were correct (infants: 3 of 7; non-infants: 6 of 15).
- Since 20 had no surgery a decline in SKF (−22±18%) was predicted and observed in 3 (infants: 1 of 5; non-infants: 2 of 15). Function in 15 remained unchanged (+1±2%), while 2 improved (+18±12%).

Thirty-four kidneys were not considered at risk due to a non-obstructive RFS:

- Nonetheless, five had surgery. Stable renal function (±0±4%) was correctly predicted in four (infants: one of one; non-infants: three of four), while it surprisingly declined in one (−13%).
- Twenty-nine did not have surgery. Stable function (±0±3%) was predicted and verified in 25 (infants: 13 of 16; non-infants: 12 of 13). One improved (+11%), but three declined (−25±21%).

An equivocal RFS occurred 38 times. The $T_{1/2}$ time and the renogram's slope were non-diagnostic in these patients.

Parameter SKF <40% (Table 5)

Forty-four kidneys were considered at risk due to a SKF< 40%:

- Therefore 21 had surgery. Improved SKF (+18±9%) was correctly predicted in 9 (infants: 3 of 6; non-infants: 6 of 15), 10 remained unchanged (±0±4%) and 2 declined (−14±2%).

Table 3 The predicted development of 98 kidneys with suspected unilateral obstruction was evaluated for the parameter TTT of ^{99m}Tc-MAG$_3$ using the algorithm shown in columns 3–5

Group	Paired studies	TTT in the baseline study	Surgery	Functional prognosis	Functional development			Correct predictions
					Better	Stable	Worse	
1A	10	Delayed	Yes	Better	8	2	0	8
1B	3	Delayed	No	Worse	0	1	2	2
1C	15	Timely	Yes	Stable	0	11	4	11
1D	70	Timely	No	Stable	4	63	3	63

Change in function by more than ±5% was assessed as better/worse

The functional development of the kidneys is presented, together with the number of correct predictions. Sixteen kidneys with indeterminate TTT are not presented, because a reasonable prediction was not possible

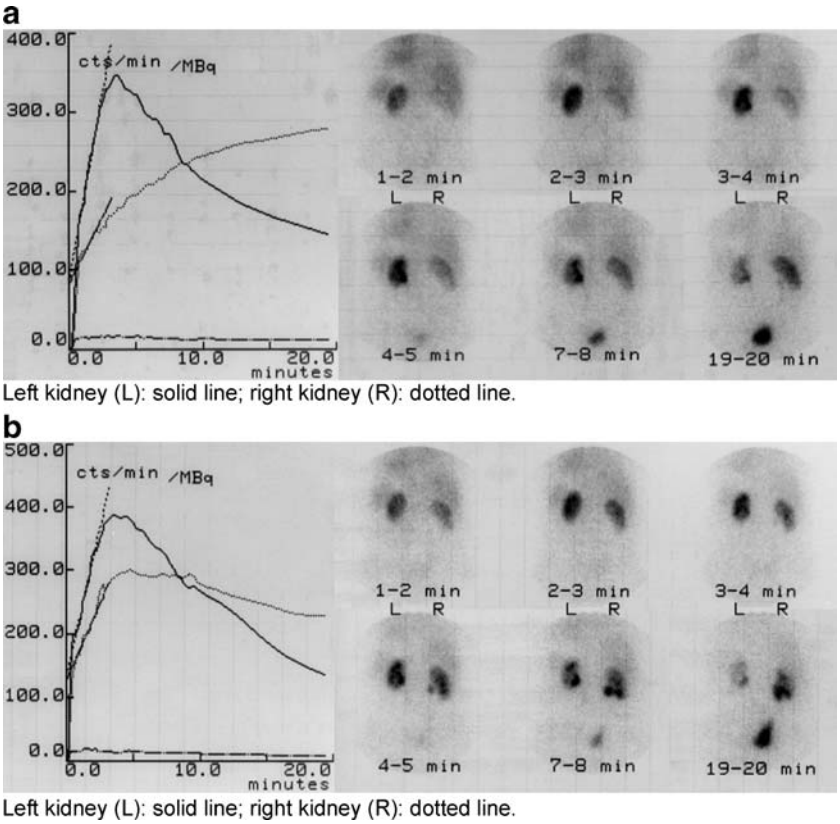

Fig. 1 **a** The ^{99m}Tc-MAG$_3$ gamma camera baseline renogram of a 65-year-old male patient with retroperitoneal fibrosis identifies right kidney obstruction with a severely compromised 17% SKF. Note the readily visible reduction of tracer uptake in the early images, while the 20-min scan demonstrates prominent tracer deposition within the parenchyma (delayed TTT). The patient went on to therapy, leading to the prognosis that the organ's SKF would improve. **b** The follow-up scintigram 87 days after baseline renography verifies the predicted increase in the right kidney's SKF, now at 40%. Transrenal tracer transit had normalized. Note the pelvic activity in the 4-min scan, more readily recognized at 5 min. The 20-min image still identifies low tracer retention in the parenchyma of both kidneys, while the enlarged renal pelvis of the formerly hydronephrotic organ is filled with activity

- Twenty-three did not have surgery. Accordingly, loss of SKF (−10±2%) was predicted, but was only observed in 3 (infants: 2 of 5; non-infants: 1 of 18). Unexpectedly 16 were unchanged (±0±3%), while 4 actually improved (+13±9%).

Seventy kidneys were not considered at risk due to a SKF≥ 40%:

- Nevertheless, 11 had surgery. Stable SKF (−1±3%) was correctly predicted for seven (infants: two of four; non-

Table 4 The predicted development of 76 kidneys with suspected unilateral obstruction was evaluated for the parameter RFS based on the algorithm shown in columns 3–5

Group	Paired studies	Response to furosemide in baseline study	Surgery	Functional prognosis	Functional development			Correct predictions
					Better	Stable	Worse	
2A	22	Obstructive	Yes	Better	9	11	2	9
2B	20	Obstructive	No	Worse	2	15	3	3
2C	5	Non-obstructive	Yes	Stable	0	4	1	4
2D	29	Non-obstructive	No	Stable	1	25	3	25

Change in function by more than ±5% was assessed as better/worse

The functional course of the kidneys is presented, together with the number of correct predictions. Thirty-eight kidneys with equivocal RFS are not presented, because a reasonable prediction is not possible

Table 5 The predicted development of 114 kidneys with suspected unilateral obstruction was evaluated for the parameter SKF<40% based on the algorithm shown in columns 3–5

Group	Paired studies	Single kidney function in the baseline study	Surgery	Functional prognosis	Functional development			Correct predictions
					Better	Stable	Worse	
3A	21	<40%	Yes	Better	9	10	2	9
3B	23	<40%	No	Worse	4	16	3	3
3C	11	≥40%	Yes	Stable	1	7	3	7
3D	59	≥40%	No	Stable	2	54	3	54

Change in function by more than ±5% was assessed as better/worse

The functional course of the kidneys is presented, together with the number of correct predictions

infants: five of seven), while three declined (−20±11%) and one improved (+8%).

- Fifty-nine remained without surgery. Stable function (±0±3%) was predicted and observed in 54 (infants: 34 of 37; non-infants: 20 of 22). Two kidneys improved (+8±2%), while three declined (−37±16%).

Discussion

Pathophysiological model

The pathophysiological model used is based on ^{99m}Tc-MAG_3 scintigraphy's ability to visualize a reduced filtration fraction (FF) [14–16]. In obstruction elevated intrapelvic pressure can cause the glomerular filtration rate (GFR) to fall, while effective renal plasma flow (ERPF) is better maintained [17, 18]. This results in a reduced FF [17, 19] and in the activation of the (particularly intrarenal) renin-angiotensin system (RAS) which seeks to re-establish the physiologically fixed relationship between GFR and ERPF (FF=0.2) [3, 6, 18–21]. When high intrapelvic pressure prevents the re-establishment of the FF, there are two consequences: (1) The washout of ^{99m}Tc-MAG_3 from the renal parenchyma is markedly delayed, visible on scintigraphic images as delayed TTT [14–16]. (2) Continuously high renin and angiotensin II (Ang II) concentrations initiate a cascade of events which include generation of transforming growth factor-β and macrophage infiltration leading to sclerosis [3, 6, 21, 22]. Additionally it was demonstrated that a delayed TTT accompanies both histomorphological restructuring and renal functional decline [9]. Accordingly a delayed TTT should identify kidneys at risk. Seremetis and Maizels [22] and Gobet et al. [21] presented corresponding models . A more detailed discussion of the pathophysiological model is presented elsewhere [9].

Relevance of TTT, RFS and SKF<40%

Delayed TTT was seen in 14 (12%) of 115 baseline renograms (Table 1). Delayed TTT identifies a disruption of the fixed relationship of ERPF and GFR and therefore requires renal pathology. In this study the pathological condition is obstruction. Accordingly, these 14 kidneys with delayed TTT were expected to show an obstructive RFS, and they did. Delayed TTT is frequently accompanied by a reversible functional decline, which may explain the observed improvement in function when SKF<40% leads to surgery [23]. Of the 14 kidneys with delayed TTT, 10 had SKF<40%, as well as surgery (Table 2). Eight improved significantly, which showed that delayed TTT identified the potential for functional improvement. The model suggests that therapy normalized both intrapelvic pressure and FF, and thereby renin and Ang II concentrations. Bajpai et al. assessed the RAS activation in patients with suspected unilateral obstruction with captopril renography and concluded that 75% of patients with RAS activation required surgery [7]. Salem et al. found that only one third of the kidneys improved functionally after pyeloplasty, even though 98% experienced improved outflow [12]. Salem et al.'s results indicate that pelvic outflow is not the primary parameter of risk in obstruction. Similarly in our population only one third (14) of the 43 kidneys with an obstructive RFS were at risk, since only they showed delayed TTT (Table 1). Accordingly only this subpopulation had a high probability of improving functionally after surgery, or of losing function without intervention. Three kidneys had delayed TTT and no surgery, and were therefore expected to deteriorate functionally. Two of these demonstrated the expected decline. Since the urologists were alerted to the risk associated with delayed TTT, this subpopulation was very small and failed to adequately support the prediction. However, an animal experimental study lends further support to the concept that delayed TTT identifies kidneys at risk [9].

In 85 paired examinations the baseline study showed timely TTT. The model predicted that kidneys with timely TTT are without risk, since the FF is within the normal range. Accordingly surgery would not be expected to improve renal function. However, 15 of the 85 kidneys were exposed to the risks of surgery (Table 3, group 1C). Surgery failed to improve renal function of this subgroup. Zucchetta et al.'s findings support this result. The authors indicated that obstructed kidneys which lack RAS activation do not improve after surgery [6]. Unexpectedly 4 of the 15 kidneys experienced functional deterioration. In three patients the loss of function appeared to be due to a progression of the underlying disease (metastatic breast cancer, rectal cancer and retroperitoneal fibrosis). In one infant there was no explanation for the unexpected deterioration. Of the 85 kidneys with timely TTT, 70 had no surgery (Table 3, group 1D). Note that 67 of these 70 kidneys (96%) maintained their function or improved. The data indicate that timely TTT is associated with very low risk. It is emphasized that timely TTT was seen in all 70 kidneys, while RFS and SKF<40% were variable (Tables 1, 2). Accordingly, only the parameter TTT identified these kidneys as being without risk. Two subgroups require a closer look. The first included nine kidneys with an *obstructive* RFS and *timely* TTT, which had no surgery. The prognoses based on the two diagnostic approaches (RFS vs TTT) were diametrically opposed. The obstructive RFS indicated functional risk, while timely TTT excluded it. Follow-up demonstrated that none of these kidneys experienced a loss of function. The second subgroup included 16 kidneys with SKF<40%, *timely* TTT and no surgery. Once again, the two prognoses (SKF<40% vs TTT) were diametrically opposed. SKF<40% indicated functional risk, but timely TTT excluded it. Follow-up demonstrated that function decreased only once. Thus, relief of obstruction based on RFS and SKF<40% would have been unnecessary. It is well known that delayed excretion during diuretic renography and low initial SKF (as well as other parameters such as degree of hydronephrosis, diuretic slope and $T_{1/2}$ time) fail to adequately predict renal function in obstruction [4, 5, 8, 24–28].

Stable or improved function was observed for the majority of 22 kidneys with obstructive RFS and surgery (Table 4, group 2A), as well as for the majority of 21 kidneys with SKF<40% and surgery (Table 5, group 3A). It therefore appeared that surgery preserved function. Nine kidneys in each group improved after surgery. TTT was delayed in eight of these and indeterminate in the ninth kidney. Note that not a single kidney with timely TTT improved after surgery. It would therefore have been possible to limit surgery to those kidneys with delayed TTT. Furthermore, the 20 non-operated kidneys with an obstructive RFS (Table 4, group 2B) and the 23 non-operated kidneys with SKF<40% (Table 5, group 3B) had a functional development nearly identical to those with surgery (groups 2A and 3A): only three kidneys from each group (2B, 3B) showed the predicted compromise.

Recognition of the kidney at risk in obstruction: diuresis renography, TTT and transit time measurements

The Consensus Report on Diuresis Renography begins with the observation that a great deal of variation exists in the techniques used, and in the interpretation of diuresis renography [10]. Diuresis renography is used to evaluate kidneys with enlarged renal pelvic systems to differentiate dilation from obstruction [11]. Diuretic renography is an important diagnostic procedure which helps to recognize the need for surgical intervention, but it fails to accurately recognize the kidney at risk [1, 2, 5–8]. 'Obstruction' does not appear to be synonymous with morphological and functional risk. A possible reason for this could be the definition of obstruction, which is dependent on the method used to recognize it. Different diagnostic procedures assess different parameters, with the consequence that the diagnosis of obstruction appears to be a 'diagnosis by inference' [29]. Britton et al. approached the problem of improving recognition of the kidney at risk by quantifying the tracer transit through the renal parenchyma [30]. They used parenchymal transit time (PTT) of ^{99m}Tc-DTPA, calculated with deconvolution analysis of ^{99m}Tc-DTPA transport through the parenchyma/tissue. Early results suggested that PTT identified 'obstructive nephropathy'. A multicentre assessment of the clinical value of dynamic renal scanning with deconvolution analysis concluded that transit times will discriminate between obstructive and non-obstructive renal disease [29]. Finally, the Consensus Report on Renal Transit Time Measurements (ISCORN) concluded that in spite of large amounts of data, only the normal transit value had been established in renal obstruction [31]. In this study we evaluated the TTT of ^{99m}Tc-MAG_3 visually. If the visual evaluation of TTT assesses the same physiology as transit times derived with deconvolution analysis, both approaches should have been effective in predicting the functional course in obstructive disease. The better results obtained with a qualitative visual approach are truly surprising. The difference in the results may be a consequence of the tracers used, as well as the fundamentally different investigative strategy which motivated the studies. Britton et al., and the other cited investigators, appear to have sought a critical transit time value in obstructive disease at which increased pressure or ischaemia lead to loss of renal function in obstruction [30, 31]. Theoretical models suggested that both ^{99m}Tc-MAG_3 and ^{99m}Tc-DTPA can be used for the

evaluation of obstruction when transit times are used [29, 31]. These models were based on the same behaviour of ^{99m}Tc-DTPA and ^{99m}Tc-MAG$_3$ at the end of the proximal tubule and appeared to assume that the physiologically fixed relationship of GFR and ERPF is always intact in obstructive disease (FF=0.2). In comparison, it was our goal to demonstrate that a reduced FF (FF<<0.2) leads to tissue reorganization and loss of function. Renal washout of ^{99m}Tc-MAG$_3$ depends on glomerular filtration while its uptake is primarily dependent on the plasma flow through peritubular vessels (~ERPF) and on the function of proximal tubular cells. Thus a reduced FF will not hinder uptake of ^{99m}Tc-MAG$_3$, but leads to its retention within the tubular lumen, visible as delayed TTT. By contrast, both renal uptake and washout of ^{99m}Tc-DTPA depend on GFR. When the FF is compromised, uptake and washout of ^{99m}Tc-DTPA are reduced. This probably makes the recognition of a reduced FF with ^{99m}Tc-DTPA impossible. That is why we used ^{99m}Tc-MAG$_3$. The disappointing results of transit time measurements documented in the ISCORN study [31] may be due to the kinetics of ^{99m}Tc-DTPA, which was used by most investigators [29–33]. We believe transit time measurements should be re-evaluated with ^{99m}Tc-MAG$_3$, since the FF appears to be abnormal in the kidneys at risk.

Limitations

When the patient population was subdivided based on renal maturation into patients in their 1st year of life and patients older than 1 year [13], the accuracy of the prognoses for the subgroups analysed was practically unchanged. Unfortunately the subgroups became so small that a detailed evaluation and comparison of the two age groups became impossible.

Due to pelvic dilatation it can be difficult to differentiate parenchymal from pelvic activity in obstructive disease, which resulted in 14% (16/115) indeterminate TTT classifications. Interestingly, when these kidneys with (initially) indeterminate TTT were reclassified as timely, the frequency of correct prognoses was nearly as good as for kidneys initially classified as having timely TTT.

The results of this study were obtained with a qualitative visual approach to assess TTT. A quantitative analysis and verification of TTT using factor analysis or pixel by pixel estimation of mean transit time would undoubtedly help gain acceptance of TTT as a diagnostic parameter.

Conclusion

TTT of ^{99m}Tc-MAG$_3$ is a parameter worthy of further investigation in predicting the functional development of (unilaterally) hydronephrotic kidneys and may improve selection for surgery. Timely TTT makes it improbable that hydronephrotic kidneys are at risk, even in the presence of an obstructive RFS or a SKF<40%. Kidneys with delayed TTT seem to have a considerable opportunity to improve after therapy, while further studies are needed to confirm their high risk of deterioration without therapy. RFS and SKF<40% were less reliable than TTT in recognizing the risk to function in obstructive renal disease.

References

1. Kaselas C, Papouis G, Grigoriadis G, Klokkaris A, Kaselas V. Pattern of renal function deterioration as a predictive factor of unilateral ureteropelvic junction obstruction treatment. Eur Urol. 2007;51:551–5.
2. Chertin B, Pollack A, Koulikov D, Rabinowitz R, Hain D, Hadas-Halpren I, et al. Conservative treatment of ureteropelvic junction obstruction in children with antenatal diagnosis of hydronephrosis: lessons learned after 16 years of follow-up. Eur Urol. 2006;49:734–8.
3. Murer L, Benetti E, Centi S, Della Vella M, Artifoni L, Capizzi A, et al. Clinical and molecular markers of chronic interstitial nephropathy in congenital unilateral ureteropelvic junction obstruction. J Urol. 2006;176:2668–73.
4. Koff SA, Binkovitz L, Coley B, Jayanthi VR. Renal pelvis volume during diuresis in children with hydronephrosis: implications for diagnosing obstruction with diuretic renography. J Urol. 2005;174:303–7.
5. Amarante J, Anderson PJ, Gordon I. Impaired drainage on diuretic renography using half-time or pelvic excretion efficiency is not a sign of obstruction in children with a prenatal diagnosis of unilateral renal pelvic dilatation. J Urol. 2003;169:1828–31.
6. Zucchetta P, Carasi C, Marzola MC, Murer L, Passerini-Glazel G, Rigamonti W, et al. Angiotensin converting enzyme inhibition worsens the excretory phase of diuretic renography for obstructive hydronephrosis. J Urol. 2001;165:2296–9.
7. Bajpai M, Puri A, Tripathi M, Maini A. Prognostic significance of captopril renography for managing congenital unilateral hydronephrosis. J Urol. 2002;168:2158–61.
8. Zaccara A, Marchetti P, la Sala E, Caione P, De Gennaro M. Are preoperative parameters of unilateral pyelo-ureteric junction obstruction in children predictive of postoperative function improvement? Scand J Urol Nephrol. 2000;34:165–8.
9. Schlotmann A, Clorius JH, Rohrschneider WK, Clorius SN, Amelung F, Becker K. Diuretic renography in hydronephrosis: delayed tissue tracer transit accompanies both functional decline and tissue reorganization. J Nucl Med. 2008;49:1196–203.
10. O'Reilly P, Aurell M, Britton K, Kletter K, Rosenthal L, Testa T. Consensus on diuresis renography for investigating the dilated upper urinary tract. Radionuclides in Nephrourology Group. Consensus Committee on Diuresis Renography. J Nucl Med. 1996;37:1872–6.
11. O'Reilly PH. Diuresis renography 8 years later: an update. J Urol. 1986;136:993–9.
12. Salem YH, Majd M, Rushton HG, Belman AB. Outcome analysis of pediatric pyeloplasty as a function of patient age, presentation and differential renal function. J Urol. 1995;154:1889–93.
13. Lythgoe MF, Gordon I, Anderson PJ. Effect of renal maturation on the clearance of technetium-99m mercaptoacetyltriglycine. Eur J Nucl Med. 1994;21:1333–7.

14. Taylor A Jr, Nally JV. Clinical applications of renal scintigraphy. AJR Am J Roentgenol. 1995;164:31–41.
15. Clorius JH, Reinbold F, Hupp T, Mandelbaum A, Schmidlin P, van Kaick G. Renovascular hypertension: a perfusion disturbance that escaped recognition. J Nucl Med. 1993;34:48–56.
16. Clorius JH, Mandelbaum A, Hupp T, Reinbold F, Zuna I, Denk S, et al. Exercise activates renal dysfunction in hypertension. Am J Hypertens. 1996;9:653–61.
17. Hvistendahl JJ, Pedersen TS, Jørgensen HH, Rehling M, Frøkiaer J. Renal hemodynamic response to gradated ureter obstruction in the pig. Nephron 1996;74:168–74.
18. Frøkiaer J, Pedersen EB, Knudsen L, Djurhuus JC. The impact of total unilateral ureteral obstruction on intrarenal angiotensin II production in the polycalyceal pig kidney. Scand J Urol Nephrol. 1992;26:289–95.
19. Guyton AC, Hall JE. Urine formation by the kidneys: I. Glomerular filtration, renal blood flow, and their control. In: Textbook of medical physiology. 11th ed. Edinburgh: Elsevier Saunders; 2006. p. 307–26.
20. Shin GT, Kim WH, Yim H, Kim MS, Kim H. Effects of suppressing intrarenal angiotensinogen on renal transforming growth factor-beta1 expression in acute ureteral obstruction. Kidney Int. 2005;67:897–908.
21. Gobet R, Park JM, Nguyen HT, Chang B, Cisek LJ, Peters CA. Renal renin-angiotensin system dysregulation caused by partial bladder outlet obstruction in fetal sheep. Kidney Int. 1999;56:1654–61.
22. Seremetis GM, Maizels M. TGF-beta mRNA expression in the renal pelvis after experimental and clinical ureteropelvic junction obstruction. J Urol. 1996;156:261–6.
23. Shokeir AA, El-Sherbiny MT, Gad HM, Dawaba M, Hafez AT, Taha MA, et al. Postnatal unilateral pelviureteral junction obstruction: impact of pyeloplasty and conservative management on renal function. Urology 2005;65:980–5.
24. Gordon I. Diuretic renography in infants with prenatal unilateral hydronephrosis: an explanation for the controversy about poor drainage. BJU Int. 2001;87:551–5.
25. Koff SA. Postnatal management of antenatal hydronephrosis using an observational approach. Urology 2000;55:609–11.
26. Eskild-Jensen A, Gordon I, Piepsz A, Frøkiaer J. Congenital unilateral hydronephrosis: a review of the impact of diuretic renography on clinical treatment. J Urol. 2005;173:1471–6.
27. Josephson S. Antenatally detected, unilateral dilatation of the renal pelvis: a critical review. 1. Postnatal non-operative treatment 20 years on—is it safe? Scand J Urol Nephrol. 2002;36:243–50.
28. Josephson S. Antenatally detected, unilateral dilatation of the renal pelvis: a critical review. 2. postnatal non-operative treatment—long-term hazards, urgent research. Scand J Urol Nephrol. 2002;36:251–9.
29. Piepsz A, Ham HR, Erbsmann F, Hall M, Diffey BL, Goggin MJ, et al. A co-operative study on the clinical value of dynamic renal scanning with deconvolution analysis. Br J Radiol. 1982;55:419–33.
30. Britton KE, Nimmon CC, Whitfield HN, Hendry WF, Wickham JE. Obstructive nephropathy: successful evaluation with radionuclides. Lancet 1979;1:905–7.
31. Durand E, Blaufox MD, Britton KE, Carlsen O, Cosgriff P, Fine E, et al. International Scientific Committee of Radionuclides in Nephrourology (ISCORN) consensus on renal transit time measurements. Semin Nucl Med. 2008;38:82–102.
32. Verboven M, Achten R, Keuppens F, Jonckheer M, Piepsz A. Radioisotopic transit parameters in obstruction of pelviureteral junction. Urology 1988;32:370–4.
33. Vivian GC, Barratt TM, Todd-Pokropek A, Gordon I. Renal parenchymal determination and analysis during dynamic 99Tcm-DTPA scans in children. Nucl Med Commun. 1984;5:35–40.