Diuretic Renography in Hydronephrosis: Delayed Tissue Tracer Transit Accompanies Both Functional Decline and Tissue Reorganization

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The significance of delayed tissue tracer transit (TTT) of ^{99m}Tc-mercaptoacetyltriglycine (^{99m}Tc-MAG3) has not been systematically evaluated in hydronephrosis. We sought to demonstrate that delayed TTT accompanies both functional decline and histomorphologic restructuring. **Methods:** Twenty 2- to 3-mo-old piglets with surgically induced partial unilateral ureteral stenosis were examined with magnetic resonance urography (MRU) to evaluate morphology and with ^{99m}Tc-MAG3 diuretic renography (DR) to determine single-kidney function (SKF), evaluate the response to furosemide stimulation (RFS), and assess TTT. All animals had DR and MRU before and after surgery and a third DR after surgery. Piglets were sacrificed after the final DR for renal histology. A total histologic score (THS) was generated. **Results:** Preoperative DR demonstrated nonobstructive RFS, timely TTT, and balanced SKF in all 20 kidneys. After ureteral ligature, MRU demonstrated pelvic dilatation in all piglets. The postoperative DRs revealed 12 kidneys with delayed TTT in one or both follow-ups. In these 12 kidneys, the SKF declined from 51% ± 4% to 18% ± 14%, and the THS was 9.0 ± 4.0. Three kidneys always had timely TTT, balanced SKF, and a THS of 1.8 ± 0.3. The contralateral, nonoperated kidneys had timely TTT and a THS of 1.2 ± 0.9. Postoperative scintigrams showed that 3 of 8 kidneys (38%) with an obstructive RFS had timely TTT, which demonstrates that TTT and RFS are not equivalent. **Conclusion:** In hydronephrosis, a delayed TTT of ^{99m}Tc-MAG3 accompanies both functional decline and histomorphologic restructuring in obstruction. According to the literature, a delayed TTT is determined by the filtration fraction of the kidneys and appears to identify an obstruction-mediated upregulated renin-angiotensin system.

Key Words: glomerular filtration rate; radioisotope renography; renin-angiotensin system; ureteral obstruction

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In hydronephrosis, tissue tracer transit (TTT) of ^{99m}Tc-mercaptoacetyltriglycine (^{99m}Tc-MAG3) has not been systematically evaluated. We demonstrate that delayed TTT accompanies both functional decline and histomorphologic restructuring. Furthermore, we present the underlying pathophysiologic model.

Delayed TTT of ^{131}I-orthoiodohippurate and ^{99m}Tc-MAG3 was investigated in patients with hypertension (*1–4*). During exercise, these tracers are trapped in the renal tissue of nearly 60% of the patients with hypertension and are visualized in sequential scintigrams of γ-camera renography. Two clinical studies with hypertensive patients demonstrated that a slow washout (delayed TTT) of these tracers is a consequence of a highly abnormal filtration fraction (FF) (FF $\ll$ 0.2) (*2,4*). In both studies, all patients with delayed TTT invariably had a selective reduction of glomerular filtration rate (GFR), whereas the effective renal plasma flow (ERPF) was comparatively well maintained. Additionally, Hvistendahl et al. showed that obstruction in pigs can lead to a 75% reduction of the GFR and to a FF of only 0.09 (*5*). In obstruction, a delayed TTT is also due to a compromised FF. This compromise was expected to activate the renin-angiotensin system (RAS) (*6*). These studies led to our hypothesis that morphologic reorganization of renal tissue in kidney disease may be the consequence of an upregulated RAS due to a low FF and recognizable by delayed TTT. Accordingly, we sought to test this hypothesis and determine whether delayed TTT of ^{99m}Tc-MAG3 signals the initiation of the cascade of events that leads to a decline in function and morphologic reorganization.

MATERIALS AND METHODS

This study was approved by the government office for animal care. Twenty 2- to 3-mo-old piglets, weighing 10–14 kg, were studied with magnetic resonance urography (MRU) to evaluate morphology and with ^{99m}Tc-MAG3 diuretic renography (DR) to

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determine single-kidney function (SKF), evaluate the excretory response to furosemide stimulation (RFS), and assess TTT. Both studies were performed on the same day.

A partial unilateral ureteral stenosis was obtained using the procedure of Koff et al. (*7*). A ligature was placed onto the proximal (5 right, 5 left) and distal (6 right, 4 left) ureter of 20 animals. General anesthesia was induced with an intramuscular injection of ketamine (10 mg/kg) and midazolam (1 mg/kg), after premedication with azaperone (4–8 mg/kg). After tracheal intubation, anesthesia continued with isoflurane while respiratory assistance was given with a mixture of oxygen and nitrous oxide. A single injection of lincomycine (20 mg/kg) was given immediately after surgery.

All animals had 3 scintigraphic examinations: the first one before the procedure, the second 6–8 d after surgery, and the third 13–27 d after surgery. One animal (animal 16) had 2 additional follow-ups, the final one on day 79. We wanted to verify that stable function is maintained in organs with timely TTT in the presence of obstruction-induced pelvic dilatation. MRU was obtained on the day of the preoperative renogram and on the day of the first postoperative renogram. The anesthetized piglets were well hydrated for DR and MRU and were sacrificed after the final examination for renal histology.

A 0.5-T MRI Gyroscan T5-NT system was used for imaging (heavily T2-weighted, 3-dimensional turbo spin-echo sequence). A tissue volume of 56–70 mm was subdivided into slices of 1.4 mm. Reformatted 3-dimensional volume images of the urinary tract were obtained. Furosemide (0.3 mg/kg) was intravenously injected 15 min before each examination; a saline infusion began concurrently. A bolus of 0.1 mmol/kg gadolinium-diethylenetriaminepentaacetic was intravenously injected during each examination.

DR was obtained after 0.444 MBq (12 μCi) of ^{99m}Tc-MAG3 per kilogram of body weight (minimum, 5.92 MBq [160 μCi]) had been intravenously injected. Twenty minutes after radiotracer injection, the examination was terminated. When pelvic excretion was delayed, the animals received 0.5 mg of furosemide per kilogram of body weight and the examination was extended for an additional 20 min (F+20 protocol). Renography was terminated after 20 min for the radiotracer administration and after 40 min for the diuretic injection. A large-field-of-view scintillation camera with a low-energy, all-purpose parallel-hole collimator was used. SKF was determined with a commercially available program. RFS was classified as obstructive, nonobstructive, or equivocal. TTT was classified as timely, delayed, or indeterminate on the basis of visual assessment. Timely TTT is defined as a physiologic transit through the tissue into the pelvis, and delayed is defined as an unphysiologic, clearly slowed transit. Parenchymal tracer transit 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 out of the tissue into the pelvis (Figs. 1–3). The following criteria indicate delayed TTT: the pelvis is visualized as being photopenic between the second and sixth or eighth minute; a relatively stable tracer distribution within the kidney over time is demonstrated (this is the case when the shape and size of the kidney remain nearly unchanged from the second or third to the eighth or 10th minute, or beyond); activity in the parenchyma increases over time and does not decrease after the second or third minute; delayed clearance of tracer out of the parenchyma into the pelvis (determined by comparing the obstructed kidney with the contralateral, healthy organ) is demonstrated; and prompt washout after furosemide excludes a delayed TTT.

For histology of the obstructed and contralateral kidneys, the following parameters were selected for evaluation: glomerulosclerosis, a decreased number of glomeruli, tubular atrophy, corticomedullary fibrosis, mononuclear cells, and vascular sclerosis. The renal tissue was stained with hematoxylin-eosin, periodic acid-schiff, and Masson-Goldner. The morphologic parameters were graded on a 7-step scale, using 0.5-step increments from 0 to 3. To simplify comparisons, these values were added to generate a total histologic score (THS). For histologic evaluation, the material was randomized to prevent tissue samples from being associated with imaging results.

RESULTS

Preoperative renography demonstrated a nonobstructive outflow pattern, timely TTT, and a balanced SKF in all animals except 2 (animals 8 and 12, which had an SKF of 40% and 60%, respectively).

Postureteral ligature MRU demonstrated pelvic dilatation in all 20 kidneys. The first postoperative DR revealed 10 kidneys (animals 1–10) with an obstructive RFS and delayed TTT (Table 1). Animal 8 died of sepsis and was therefore removed from the evaluation (Table 2). The SKFs of the remaining 9 kidneys declined from 50.9% ± 2.5% to 21.1% ± 8.5%. Of these 9 kidneys, the second postoperative DR showed that 3 (animals 4–6) were silent (SKF declined from 15.0% ± 13.2% to 0%) and had a THS of 13.7% ± 2.1%. Three others (animals 1–3) continued with an obstructive RFS and a delayed TTT. Their SKF declined from 26.0% ± 1.0% to 14.7% ± 8.1%, with a THS of 7.0 ± 1.8. Another 2 animals (animals 7 and 10) continued with obstruction, whereas TTT normalized and SKF remained stable (20.0% ± 0.0%), with a THS of 9.0 ± 1.4. Animal 9 had delayed TTT in the first postoperative examination and was declamped. In the final examination, RFS and TTT had normalized, SKF improved from 27% to 45%, and THS was 7.0.

The first postoperative DR of kidneys 11–20 revealed a nonobstructive RFS and timely TTT, despite the pelvic dilatation seen on MRU. Four kidneys had to be removed from the evaluation because of urinary leak (animal 17), infection at the site of the ligature (animal 19), sepsis (animal 20), and no histologic data due to a technical problem (animal 18) (Table 2).

The following results were documented for the remaining 6 kidneys (11–16). SKF remained stable (−0.5% ± 2.3%) during the interval between the preoperative and the first postoperative examination. The second postoperative DR showed that 2 kidneys (animals 12 and 14) developed an obstructive RFS and a delayed TTT after the stenoses had been increased surgically. The SKF in animals 12 and 14 was reduced to 29% and 21%, respectively; they had THSs of 13.5 and 10.5, respectively. Animal 15 developed an obstructive RFS and delayed TTT spontaneously, lost 24% SKF, and had a THS of only 1.5. Three kidneys (animals 11, 13, and 16) maintained a timely TTT, whereas SKF was stable (−1.0% ± 1.0%). Their THS was 1.8 ± 0.3.

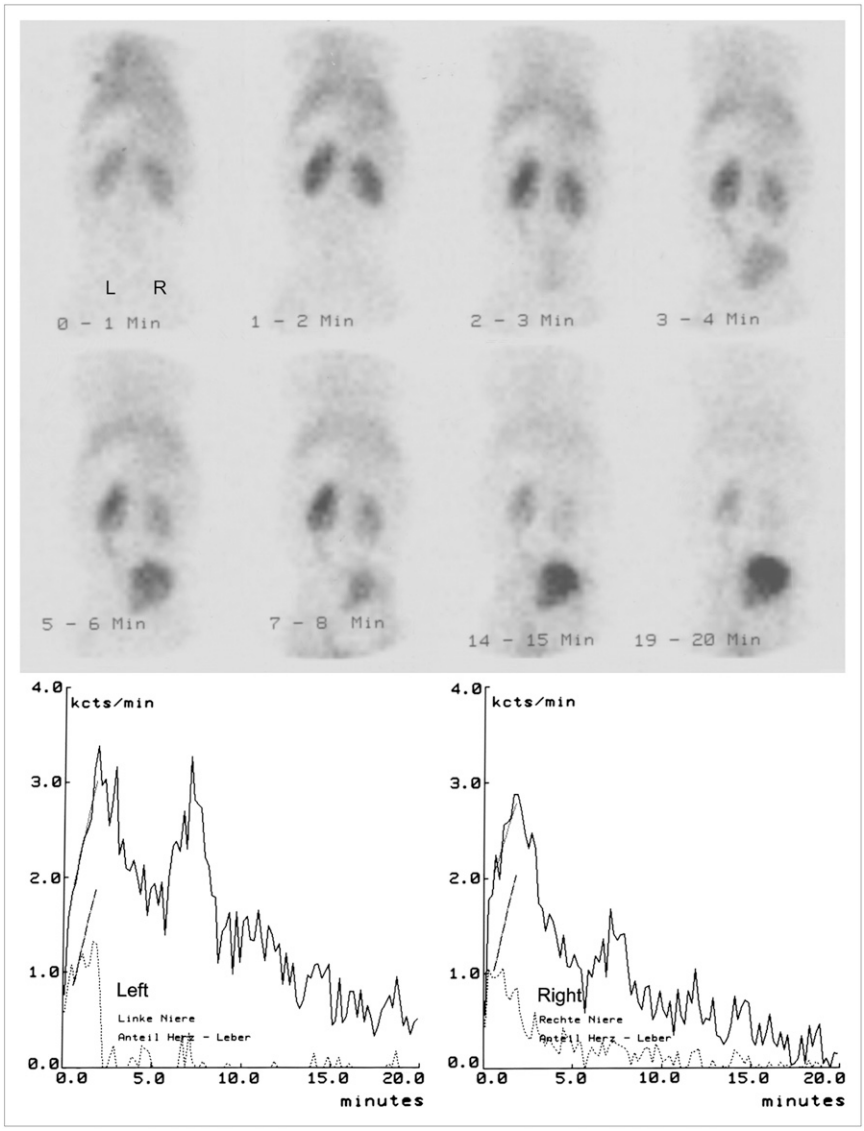

FIGURE 1. Preoperative study identified normal renograms for both kidneys. Note spike due to movement artifact. Single-kidney contribution to total function was 52% (left) and 48% (right). Pelvic activity was clearly recognizable during third minute. At 20th min, tracer excretion was nearly complete. After scintigraphy, ligature was placed around right ureter.

However, the RFS diverged in these 3 kidneys: in animals 11 and 13, the RFS remained nonobstructive, whereas in animal 16, the RFS changed from nonobstructive to equivocal. With a timely TTT and an equivocal RFS, the SKF of animal 16 remained stable during the extended observation period of 79 d. The mean THS of all 12 kidneys, with a delayed TTT in one or both follow-up examinations, was 9.0 ± 4.0. The contralateral nonoperated kidneys always had a timely TTT and a nonobstructive RFS. Their mean THS was 1.2 ± 0.9 (Table 1).

DISCUSSION

Delayed TTT of tracers cleared by tubular secretion (^{99m}Tc-MAG3 and ^{131}I-orthoiodohippurate) identifies a marked reduction of the filtration fraction (FF $\ll$ 0.2) (*2,4,8*), which is a consequence of a pronounced reduction of the GFR (ERPF is less reduced). The pathophysiologic correlate of a delayed washout of ^{99m}Tc-MAG3 from the renal tissue (delayed TTT) was initially described for the exercise renogram (*1*) and later verified (*2,4*). Taylor and Nally also attributed delayed TTT during captopril renography to a pharmacologically mediated, pronounced reduction of the GFR (*8*). Physiologically, tracers cleared by tubular secretion are deposited in the tubular lumen. This deposition depends on the plasma flow through peritubular vessels (approximately ERPF) and not on glomerular filtration. After deposition in the tubulus lumen, the tracer is transported through and washed out of the lumen by the glomerular filtrate. The washout rate depends on glomerular filtration, not on plasma flow through peritubular vessels (~ERPF). Accordingly, a significantly reduced GFR will slow the washout from the tubulus lumen. The accumulated tracer is then visualized on the ^{99m}Tc-MAG3 scintigram as delayed TTT. These images of compromised FF are not disease-specific. They can also be seen in acute transplant rejection,

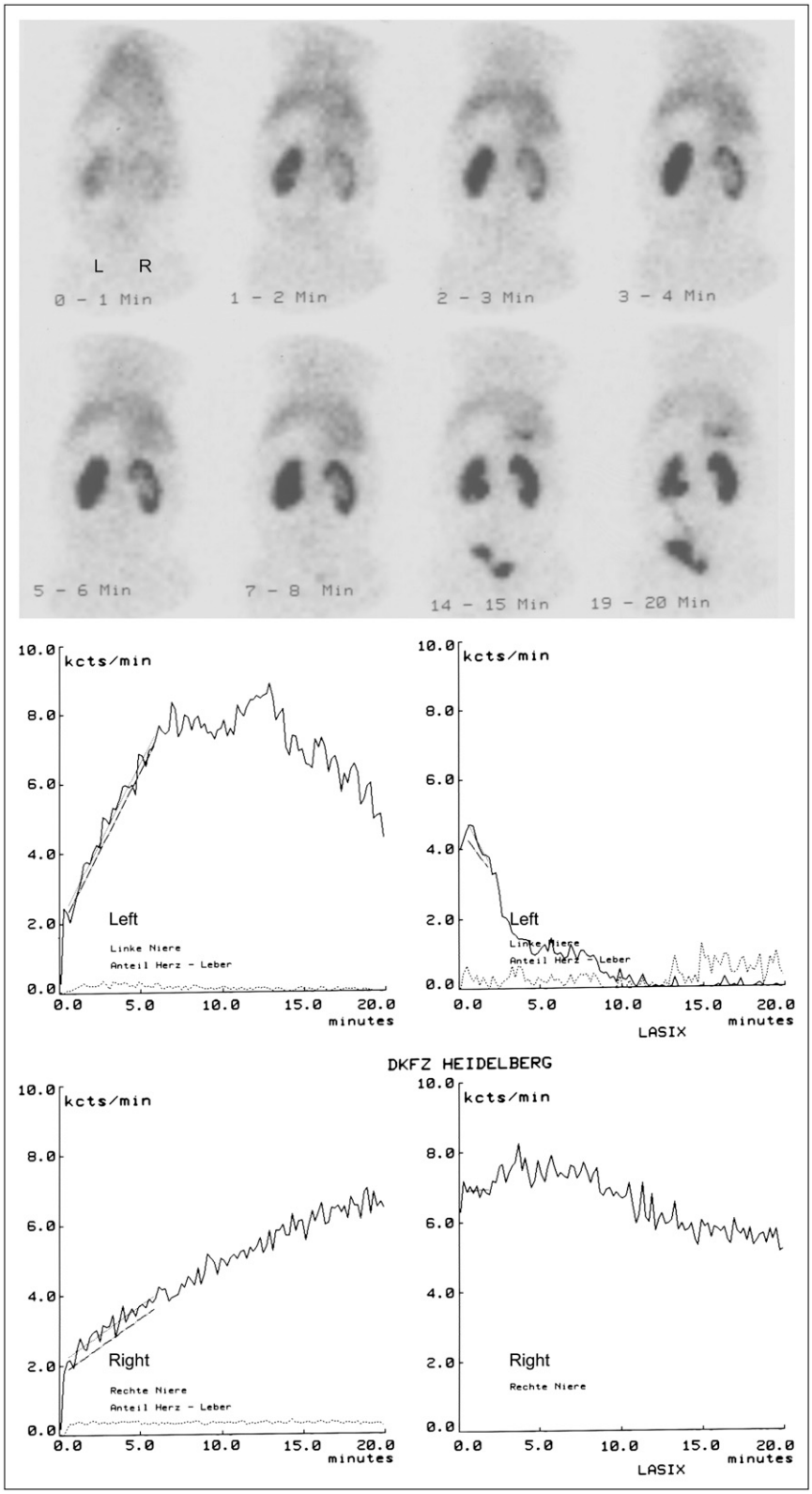

FIGURE 2. At 7 d after obstruction, split renal function was 74% (left) and 26% (right). Left kidney showed nonobstructive functional excretion disturbance with prompt washout after furosemide. In right kidney, tissue activity increased continuously from second to 20th minute. Note lack of tracer deposition within renal pelvis. Delayed TTT indicated that continuation of functional deterioration should be expected.

posttransplant acute tubular necrosis, and a positive captopril renogram (*8,9*). We know of no other imaging approach that recognizes a compromised FF. In a related approach, Bajpai et al. used captopril renography to identify patients with activation of the RAS in hydronephrosis (*10*).

The tested pathophysiologic model assumed the following:

- Renal obstruction increases pressure within the renal pelvis, which may cause glomerular filtration to fall (*5,11–13*), resulting in a reduced FF (FF $\ll$ 0.2) (*5*)

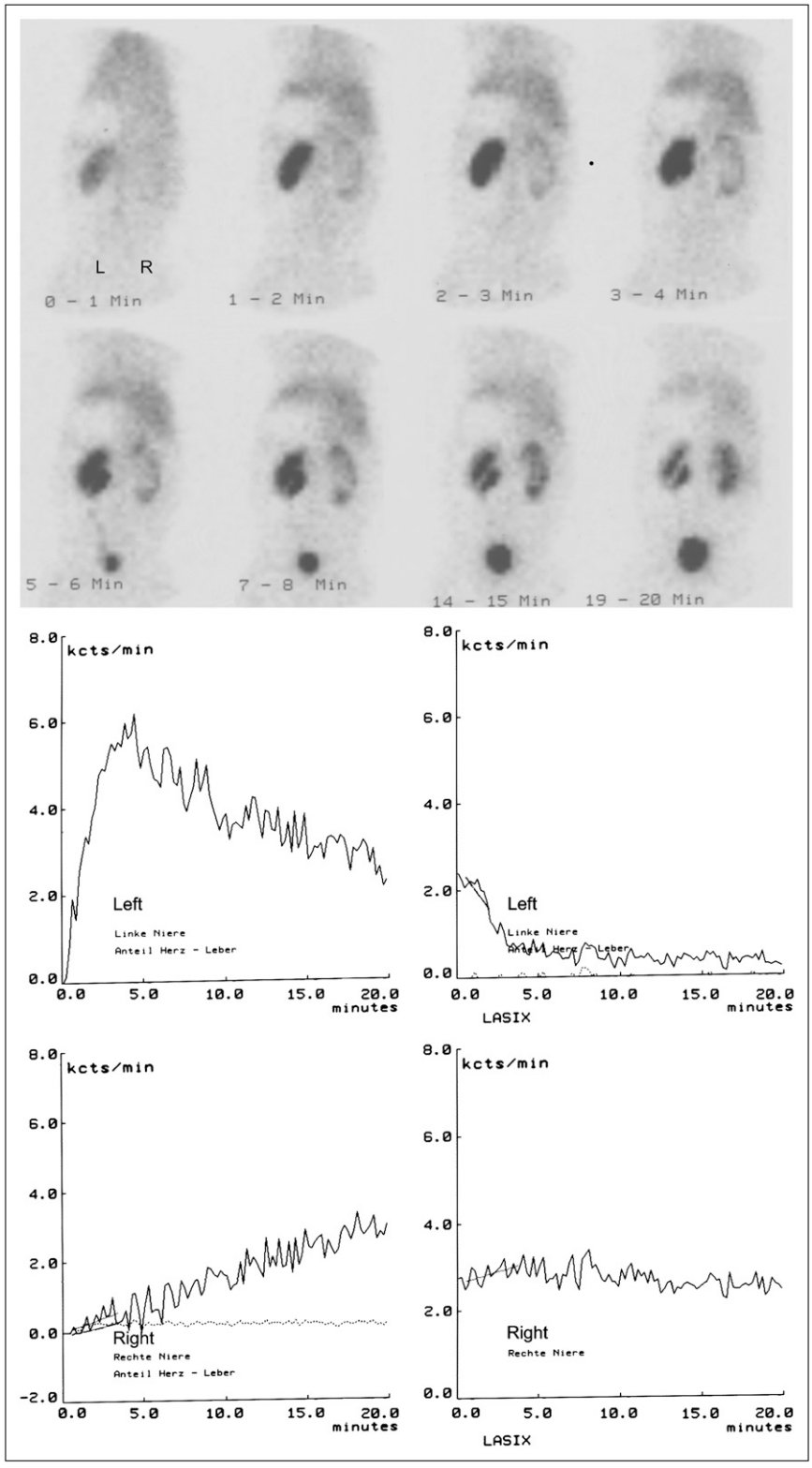

FIGURE 3. At 14 d after obstruction, split renal function was 90% (left) and 10% (right). Left kidney demonstrated physiologic function. Pelvic activity was recognized during third minute and was prominently seen during fourth minute. At 20 min, pelvis contained remnants of tracer. Obstructed right kidney appeared enlarged. Tracer uptake was reduced, compared with uptake demonstrated at 7 d after obstruction. Pelvic activity was not seen before 20th minute. Response to furosemide stimulation showed obstructive outflow pattern.

recognized by delayed TTT. Hvistendahl et al. demonstrated that the initiation of obstruction in pigs can lead to a 75% reduction of the GFR and to a FF of only 0.09 at maximum pressure (*5*).

- A compromised FF results in the activation of the intrarenal RAS (*13–16*).
- When a high angiotensin II (Ang II) concentration fails to reestablish the FF, the washout of tracers

TABLE 1
Data for 15 Kidneys with Surgically Induced, Unilateral Ureteric Stenosis and 15 Contralateral, Nonoperated Kidneys

Grouped kidneys	TTT at follow-up: First post-OP	TTT at follow-up: Second post-OP	No.	Split renal function ± SD (%): Pre-OP	Split renal function ± SD (%): First post-OP	Split renal function ± SD (%): Second post-OP	THS ± SD	Mean histologic scores: Glomerulosclerosis	Decreased glomeruli	Tubular atrophy	Corticomedullary fibrosis	Mononuclear cells	Vascular sclerosis
1 to 6	Delayed	Delayed	6	52 ± 3	21 ± 10	7 ± 10	10.3 ± 4.0	0.9	1.8	2.2	2.7	1.6	1.3
7, 9, 10	Delayed	Timely	3	50 ± 1	22 ± 4	28 ± 14	8.3 ± 1.5	0.5	1.3	1.7	2.3	1.5	1.2
12, 14, 15	Timely	Delayed	3	52 ± 8	52 ± 7	27 ± 3	8.5 ± 6.2	0.0	1.7	1.7	2.2	2.0	1.0
11, 13, 16	Timely	Timely	3	47 ± 3	46 ± 4	47 ± 3	1.8 ± 0.3	0.2	0.0	0.2	1.0	0.5	0.0
Contralateral	Timely	Timely	15	—	—	—	1.2 ± 0.9	0.1	0.0	0.7	0.2	0.2	0.0

OP = surgery.

Kidneys with surgically induced, unilateral ureteric stenosis were grouped based on TTT at time of first and second post-OP renograms. Histologic parameters selected included glomerulosclerosis, decreased number of glomeruli, tubular atrophy, corticomedullary fibrosis, mononuclear cells, and vascular sclerosis. Seven-step scale with 0.5-step increments from 0 to 3 was used to grade histology. For comparison, these values were added to generate THS.

cleared by tubular secretion (^{99m}Tc-MAG3) from the renal tissue is markedly delayed, visible on scintigraphic images as delayed TTT (*2,4,8*). In addition, nephrons exposed to a continuously activated RAS experience morphologic reorganization and eventually sclerosis mediated by transforming growth factor-β (TGF-β), which is directly stimulated by renin as well as Ang II (*17–20*).

- Accordingly, a delayed TTT of ^{99m}Tc-MAG3 should identify those kidneys whose function is at risk.
- After release of obstruction, the FF normalizes, which downregulates the RAS.
- The model also suggests that obstructed kidneys with a timely TTT, equivalent to a normal FF, are not exposed to the risk of morphologic reorganization. Accordingly, they do not require relief of obstruction.

The pathophysiologic models of Gobet and Seremetis are comparable to our model. Gobet et al. (*21*) presented a model that describes the effects of obstruction on the renal RAS and on histology, and Seremetis et al. (*22*) sketched the molecular mechanisms during obstruction involving TGF-β. The models of Gobet and Seremetis did not deal with FF, GFR, ERPF, and TTT; therefore, an important pathophysiologic link, and a method for recognizing the kidney at risk, was not presented.

Another approach was that of Britton et al. (*23*). In 1979, Britton used parenchymal transit time (PTT), calculated by deconvolution analysis of diethylenetriaminepentaacetic transport through the parenchyma, to assess obstruction. Prolonged PTT indicated the necessity to relieve obstruction. Posttherapy PTT and SKF improved. Eight years later, Britton et al. compared analyses of RFS and PTT (*24*). A thoughtful evaluation of both techniques, based on 63 patients, suggested that the combined use of RFS and PTT improved assessment of obstruction. A study by Bahar et al. concluded that PTT cannot predict the outcome of

TABLE 2
Data for 5 Kidneys Excluded Due to Complications

Animal no.	Pre-OP DR	Pre-OP TTT	Pre-OP SKF (%)	Post-OP MRU	1st Post-OP DR	1st Post-OP TTT	1st Post-OP SKF (%)	2nd Post-OP DR	2nd Post-OP TTT	2nd Post-OP SKF (%)	THS
8	Not obstr	Timely	40	Dilated	Obstr	Delayed	10	Obstr	Timely	23	—
17	Not obstr	Timely	53	Dilated	Equiv	Timely	48	Equiv	Timely	41	7.0
18	Not obstr	Timely	47	Dilated	Equiv	Timely	53	Equiv	Timely	48	—
19	Not obstr	Timely	50	Dilated	Equiv	Timely	39	Died	—	—	2.5
20	Not obstr	Timely	50	Dilated	Equiv	Timely	38	Died	—	—	8.5

OP = surgery; obstr = obstructed; equiv = equivocal.

Five kidneys were excluded from the evaluation of kidneys (presented in Table 1) after complications. Histologic parameters selected included glomerulosclerosis, decreased number of glomeruli, tubular atrophy, corticomedullary fibrosis, mononuclear cells, and vascular sclerosis. Seven-step scale with 0.5-step increments from 0 to 3 was used to grade histology. For comparison, these values were added to generate THS. Animal 8: sepsis, spontaneous tracer transit change, no histologic data available; animal 17: urinary leak; animal 18: no histologic data available; animals 19 and 20: died before final renogram (animal 19: ligature inflammation, animal 20: sepsis).

surgery; however, 2 other parameters (SKF and the extraction slope) are effective (*25*). Because PTT appears to assess the same physiology as the visual evaluation of TTT, we suspect that PTT based on deconvolution analysis will also be effective in predicting the functional course in obstructive disease.

The results demonstrated that a marked functional decline occurs when delayed TTT accompanies obstruction (Table 1). When delayed TTT was seen in the first postoperative scintigram, functional decline was also seen only at that time. The same was true for the second postoperative scintigram and for both postoperative scintigrams (Table 1). As predicted by the model, a delayed TTT occurred only in association with an obstructive RFS; therefore, a delayed TTT required obstruction. However, it should not be concluded that TTT and RFS are equivalent parameters. This was readily recognized in the second postoperative examinations, which showed that 3 of 8 (38%) kidneys had timely TTT but an obstructive RFS. Furthermore, 2 of these 3 kidneys had no further decline in function, whereas the third one even improved during obstruction. Thus, obstruction will not necessarily cause TTT to be delayed. Furthermore, our results demonstrated pronounced histologic changes in kidneys with delayed TTT, compared with minor or nearly lacking histologic changes in those kidneys with timely TTT. The mean THS of kidneys with a delayed TTT was 9.0 ± 4.0, varying from 8.3 ± 1.5 to 10.3 ± 4.0, depending on the point in time when the delayed TTT was diagnosed (Table 1). Operated kidneys with timely TTT had a mean THS of only 1.8 and the contralateral nonoperated kidneys only 1.2 (Table 1). Murer et al. found a similar correlation between histologic changes and SKF and diuretic drainage pattern (*26*). TTT was not evaluated. The almost unchanged histology of 1 obstructed kidney (animal 15) surprised us because TTT was delayed and function declined in the second postoperative scintigram. The only explanation offered for this finding is based on the spontaneous change in TTT from timely to delayed. It is suspected that the TTT disturbance began during the final days of the study, leading to functional compromise but lacking adequate time for tissue reorganization.

An activated renal RAS as an initial step leading to nephrosclerosis in obstruction is widely supported by the literature: The key role of the intrarenal RAS was investigated in detail (*14,16*). Ureteral obstruction causes renin secretion to rise (*21,27,28*). Huang et al. showed that the direct upregulation of TGF-β by renin is independent of Ang II (*17*). Numerous authors implicated Ang II directly and indirectly through its influence on TGF-β as relevant in the pathogenesis of tubulointerstitial fibrosis: Gobet et al. concluded that TGF-β, as a mediator of Ang II, could induce and propagate interstitial fibrosis (*21*). The immunohistochemical analyses of Murer et al. also confirmed the role of the RAS (and TGF-β) in the fibrogenic response (*26*). Shin et al. concluded that suppression of the independent intrarenal RAS prevents the formation of renal TGF-β and other factors (*14*). Ishidoya et al. showed the importance that the RAS has for renal fibrosis, using an Ang II receptor antagonist and an ACE inhibitor for its suppression (*18*). Frokiaer et al. demonstrated in pigs that ureteral ligature results in elevated ipsilateral intrarenal Ang II generation (*13,15*). Yoo et al. (*19*), Kagami et al. (*20*), and Pimentel et al. (*29*) reported that the elevated TGF-β seen in obstruction is mediated by Ang II. Infusions of Ang II are reported to cause interstitial and glomerular lesions, which lead to fibrosis (*19,20*). Pimentel et al. believed that Ang II has a central role in initiating renal fibrosis, both in ureteral obstruction and other tubulointerstitial diseases (*29*). Thus, it is not surprising that interstitial fibrosis in chronic renal disease is suppressed by inhibition of several components of the RAS: angiotensinogen (*14,30*), Ang II (*20*) and its receptor (*18,29*), and angiotensin-converting enzyme (*18,28*). Indeed, Fern et al. believe that 50% of the interstitial fibrotic response seen in obstruction is a consequence of Ang II generation (*30*). They believe, as we do, that Ang II–induced fibrosis is a general mechanism of progression in multiple renal diseases. The progression to terminal renal failure so typical of obstruction and other diseases of the kidney, appears to be the consequence of intrarenal renin and Ang II generation (*13,14,17,18,20,21*).

CONCLUSION

Delayed tissue tracer transit (TTT) accompanies both renal functional decline and histomorphologic restructuring in hydronephrosis. This appears to be a consequence of an activated renin-angiotensin system (RAS).

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