$^{99m}$Tc-MAG3 Tissue Tracer Transit:

A Basic Diagnostic Parameter of Renal Disease?

J.H. Clorius
Heidelberg, Germany
1976: Search for a renal function disturbance of EH

- Thoughtful search, but without a clear concept
- Included: personal and family hypertension history
- Documentation of antihypertensive drugs
- Two examinations whenever possible
1981: Posture dependent retention of hippurate in hypertension

- Relevance of sympathetic nervous system activity (Esler, Hollenberg, Zanchetti)

- Continue with exercise to increase sympathetic NS activity
1983: Exercise Renography

- Exercise mediated retention of hippurate
- 55-60% of all hypertensives!
- Normotensives: uninfluenced
Supine Renography
Exercise Renography
Supine Renography
Exercise Renography
Renal tracer kinetics

- FF compromise causes $^{99m}$Tc-MAG3 tracer retention
Physiologic model

• SNS
  → afferent vessel constriction
  → reduced glomerular filtration
  → single nephron GFR down

• Efferent vessel flow better maintained
  → tracer delivered to cell
  → cell / lumen conc. gradient compromised
  → image of ‘tissue tracer accumulation’
1993: Clearance

- Exercise can cause FF compromise
• Hollenberg:
  Clarify relationship between renal function and morphology in EH
• Does FF compromise cause nephron sclerosis?
Sealey’s hypothesis

• A morphologic hypothesis

Sealey JE, Blumenfeld JD, Bell GM, Pecker MS, Sommers SC, Laragh JH.
On the renal basis for essential hypertension: nephron heterogeneity with discordant renin secretion and sodium excretion causing a hypertensive vasoconstriction-volume relationship.
J Hypertens. 1988 Oct;6(10):763-77
Comparing Sealey’s Hypothesis with the data from Clorius

<table>
<thead>
<tr>
<th></th>
<th>Sealey</th>
<th>Clorius</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothesis based on</td>
<td>nephron morphology</td>
<td>nephron function</td>
</tr>
<tr>
<td>Assumed nephron</td>
<td>two stable populations: nephrons remain in</td>
<td>two unstable populations: posture and physical activity determine the</td>
</tr>
<tr>
<td>populations</td>
<td>the same population</td>
<td>population in which nephrons reside</td>
</tr>
<tr>
<td>Population 1</td>
<td>normal nephrons: hyperfiltering, hypernatriuretic</td>
<td>normal nephrons: hyperfiltering, hypernatriuretic</td>
</tr>
<tr>
<td>Population 2</td>
<td>sclerotic nephrons: excessive renin secretion causes EH</td>
<td>nephrons with FF-compromise: excessive renin secretion causes EH and nephron sclerosis</td>
</tr>
<tr>
<td>The sclerotic</td>
<td>explained excess renin secretion</td>
<td>not required for EH</td>
</tr>
<tr>
<td>nephron</td>
<td>genesis unknown</td>
<td>genesis explained</td>
</tr>
</tbody>
</table>
RENAL TISSUE TRACER TRANSIT (TTT) IN HYDRONEPHROSIS:

PATHOPHYSIOLOGY AND CLINICAL UTILITY

A. Schlotmann
Freiburg, Germany
TTT in HYDRONEPHROSIS

Does a FF-compromise
(= delayed tissue tracer transit)
cause nephron sclerosis and functional compromise?

=> Obstruction model
TTT in HYDRONEPHROSIS

1. Clinical study
2. Animal experimental study
3. Pathophysicsology
4. Conclusions
5. Outlook

TTT in HYDRONEPHROSIS

1. Clinical Study

• **Aim:**
  Prediction of single kidney function (SKF) of kidneys with suspected unilateral obstruction
  - ‘better’, ‘worse’, or ‘stable’ single kidney function (SKF), cut-off $\Delta > 5\%$
  - 2 independent predictions based on
    1. Tissue Tracer Transit (TTT) of $^{99m}$Tc-MAG3
      in comparison with
    2. Response to Furosemide Stimulation (RFS)
[3. Single Kidney Function <40% (SKF<40%)]
By focusing on functional development, there was no need for a gold standard in the diagnostics of obstruction.
Methods: Patients and examinations

• 169 $^{99m}$Tc-MAG3 diuretic renograms of 50 patients were retrospectively evaluated
  
  – suspected unilateral obstruction (radiologic or ultrasound)
  
  – normal contralateral kidney

  – patient with more than two examinations:
    examinations served as baseline and as follow-up

=> 115 paired (baseline/follow-up) $^{99m}$Tc-MAG3 renograms
Methods: Renography

- adults 0.37 MBq $^{99m}$Tc-MAG3/kg body weight
- children 2.59 MBq $^{99m}$Tc-MAG3/kg body weight

- first 18 months F+10, afterwards F+20 protocol

- Furosemide: 0.5 mg/kg (maximum 40 mg) in adults, 1.0 mg/kg (maximum 20 mg) in children

- large field of view camera (Siemens e.cam) with a low-energy, all-purpose Collimator

- 20 min: 5 s/frame for 3 min, 10 s/frame for 7 min and 30 s/frame for 10 min

- one minute scintiscans at 1-5, 8, 10, 15, 19 and 20 min final 1-min scintiscan after micturition
Methods: Parameters to predict SKF

- tissue tracer transit (TTT)
  - timely, delayed or indeterminate
    - visually assessed by two experienced nuclear medicine specialists

- response to furosemide stimulation (RFS)
  - non obstructive, obstructive or equivocal
Methods: Criteria for delayed TTT

(1) pelvis photopenic between the 2nd and 6th/8th min

(2) relatively stable tracer distribution within the kidney over time
   => shape and size of kidney nearly unchanged
       from 2\textsuperscript{nd}/3\textsuperscript{rd} min to the 8\textsuperscript{th}/10\textsuperscript{th} min, or beyond

(3) activity in the parenchyma increases with time,
    or does not decrease adequately after 2\textsuperscript{nd}/3\textsuperscript{rd} min

(4) delayed clearance into the pelvis
   => comparing hydronephrotic with contralateral kidney
      – obstructed kidney appears enlarged in late images due to tracer retention in the periphery of
        the parenchyma
      – later appearance of tracer in the pelvis of the obstructed kidney, compared to the non-
        obstructed kidney
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.

<table>
<thead>
<tr>
<th>Group</th>
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<th>Surgery</th>
<th>Functional prognosis</th>
<th>Functional development</th>
<th>Correct predictions</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Delayed</td>
<td>Yes</td>
<td>Better</td>
<td>Better</td>
<td>8</td>
</tr>
<tr>
<td>1A</td>
<td>10</td>
<td>Delayed</td>
<td>No</td>
<td>Worse</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>1B</td>
<td>3</td>
<td>Timely</td>
<td>Yes</td>
<td>Stable</td>
<td>0</td>
<td>11</td>
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<tr>
<td>1C</td>
<td>15</td>
<td>Timely</td>
<td>No</td>
<td>Stable</td>
<td>4</td>
<td>63</td>
</tr>
<tr>
<td>1D</td>
<td>70</td>
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<td>0 2 0 8</td>
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<td>0 1 2 2</td>
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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.
Methods: Prognosis based on RFS

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.

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<tr>
<td></td>
<td></td>
<td>Obstructive</td>
<td>Yes</td>
<td>Better</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Obstructive</td>
<td>No</td>
<td>Worse</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>2A</td>
<td>22</td>
<td>Obstructive</td>
<td>No</td>
<td>Stable</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>2B</td>
<td>20</td>
<td>Obstructive</td>
<td>Yes</td>
<td>Stable</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>2C</td>
<td>5</td>
<td>Non-obstructive</td>
<td>Yes</td>
<td>Stable</td>
<td></td>
<td>1</td>
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<tr>
<td>2D</td>
<td>29</td>
<td>Non-obstructive</td>
<td>No</td>
<td>Stable</td>
<td></td>
<td>1</td>
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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.
Results: Differences in the evaluation of TTT between the two observers

• 27 divergent results out of 169 examinations
  – consensus discussion => single response

• 24 slight differences
  – one reviewer: timely or delayed TTT vs
  – other reviewer: indeterminate TTT

• only 3 times clearly divergent
  – timely vs delayed TTT
Results: TTT and RFS

\(^{99}\text{mTc-MAG}_3\) diuretic scintigraphy of 115 kidneys with suspected obstruction

<table>
<thead>
<tr>
<th>Tissue tracer transit</th>
<th>Response to furosemide stimulation</th>
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<tr>
<td></td>
<td>Obstructive</td>
</tr>
<tr>
<td>Delayed</td>
<td>14</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>14</td>
</tr>
<tr>
<td>Timely</td>
<td>15</td>
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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.
Results: Prognoses based on TTT

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.

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<td>1D</td>
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<tr>
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<td>Yes</td>
<td>Stable</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>2D</td>
<td>29</td>
<td>Non-obstructive</td>
<td>No</td>
<td>Stable</td>
<td>1</td>
<td>25</td>
</tr>
</tbody>
</table>

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.
Results: Analysis of a subgroup

- 9 kidneys:
  - timely TTT
  - obstructive RFS
  - no surgery

=> two diametrically opposed prognoses:
  - based on timely TTT: no functional risk
  - based on obstructive RFS: functional risk

- follow-up: no kidney had a loss of function
  => obstructive RFS did not indicate risk
Does surgery *preserve* function in case of obstructive RFS?

- 22 kidneys: obstructive RFS, surgery
  => only 2 kidneys lost function

- 20 kidneys: obstructive RFS, no surgery
  => only 3 kidneys lost function

⇒ same result with and without surgery

⇒ limit surgery to kidneys with delayed TTT
TTT in HYDRONEPHROSIS

2. Animal Experimental Study

Does delayed TTT accompany both functional decline and histomorphologic restructuring?
Methods

• twenty 2- to 3-mo-old piglets

• surgically induced partial unilateral ureteral stenosis

• $^{99m}$Tc-MAG3 diuretic renography (DR) and magnetic resonance urography (MRU)
  – before and after surgery
  – third DR after surgery

• piglets sacrificed after final DR for renal histology
  – total histologic score (THS)
Methods: Diuretic Renography

- **TTT** classified as timely, delayed, or indeterminate (visually assessed)
- **RFS** classified as obstructive, nonobstructive, or equivocal

  - 0.444 MBq (12 mCi) $^{99mTc}$-MAG3 per kg body weight (minimum, 5.92 MBq [160 mCi])
  - 20 min examination
  - when pelvic excretion delayed, 0.5 mg of furosemide per kg body weight, and additional 20 min (F+20)
  - large-field-of-view scintillation camera with a low-energy, all-purpose parallel-hole collimator
Methods: Histology

- tissue stained with hematoxylin-eosin, periodic acid-Schiff, and Masson-Goldner

- 7 parameters:
  - glomerulosclerosis
  - number of glomeruli
  - tubular atrophy
  - corticomedullary fibrosis
  - mononuclear cells
  - vascular sclerosis

  - score from 0 to 3 (0.5-step increments)
    => added to a total histologic score (THS) for comparison
### Results: Functional and morphologic development

**TABLE 1**
15 kidneys with surgically induced, unilateral ureteric stenosis and 15 contralateral, nonoperated kidneys

<table>
<thead>
<tr>
<th>Grouped kidneys</th>
<th>TTT at follow-up</th>
<th>Split renal function ± SD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First post-OP</td>
<td>Second post-OP</td>
</tr>
<tr>
<td>1 to 6</td>
<td>Delayed Delayed</td>
<td>6</td>
</tr>
<tr>
<td>7, 9, 10</td>
<td>Delayed Timely</td>
<td>3</td>
</tr>
<tr>
<td>12, 14, 15</td>
<td>Timely Delayed</td>
<td>3</td>
</tr>
<tr>
<td>11, 13, 16</td>
<td>Timely Timely</td>
<td>3</td>
</tr>
<tr>
<td>Contralateral</td>
<td>Timely Timely</td>
<td>15</td>
</tr>
</tbody>
</table>

OP = surgery.
TTT in HYDRONEPHROSIS

3. Pathophysiology: model

Outflow stenosis

=> pressure within the renal pelvis ↑

=> GFR ↓ and FF ↓

=> (intrarenal) Renin-Angiotensin-System (RAS) ↑
TTT in HYDRONEPHROSIS

3. Pathophysiology: model

RAS ↑↑

either:
- high Ang II concentration reestablishes FF
  - timely TTT

or:
- FF cannot be reestablished
  - delayed TTT
  - high Renin, high Ang II
  - eventually morphologic reorganization and sclerosis

⇒ delayed TTT of \(^{99m}\)Tc-MAG3 should identify kidneys at risk
TTT in HYDRONEPHROSIS

3. Pathophysiology: literature

• pressure within the renal pelvis ↑
  => GFR ↓ and FF ↓

  • Hvistendahl JJ et al. 1996
    – 75% reduction of GFR, FF only 0.09 at maximum pressure
  • Chen CF et al. Neurourol Urodyn. 2001
  • Chevalier RL et al. Kidney Int. 2000
  • Frokiaer J et al. Scand J Urol Nephrol. 1992
TTT in HYDRONEPHROSIS

3. Pathophysiology: literature

- GFR ↓ and FF ↓ = delayed TTT
  - Taylor A Jr et al. AJR. 1995
TTT in HYDRONEPHROSIS

3. Pathophysiology: literature

• activated (renal) RAS as initial step leading to nephrosclerosis in obstruction
  – ureteral obstruction => Renin ↑, Ang II ↑

  • Frokiaer J et al. Scand J Urol Nephrol. 1992
  • Gobet R et al. Kidney Int. 1999
  • Ayan S et al. Urology. 2001
  • Berka JL et al. J Hypertens. 1994
TTT in HYDRONEPHROSIS

3. Pathophysiology: literature

- activated (renal) RAS as initial step leading to nephrosclerosis in obstruction
  - upregulation of TGF-β by Renin and Ang II

  - Huang Y et al. Kidney Int. 2006
  - Yoo KH et al. Am J Hypertens. 1998
TTT in HYDRONEPHROSIS

3. Pathophysiology: literature

• activated (renal) RAS as initial step leading to nephrosclerosis in obstruction
  – Ang II => fibrosis via TGF-β etc.
  • Yoo KH et al. Am J Hypertens. 1998
  • Gobet R et al. Kidney Int. 1999
  • Murer L et al. J Urol. 2006
  • Pimentel JL Jr et al. Kidney Int. 1995
  • Fern RJ et al. J Clin Invest. 1999
TTT in HYDRONEPHROSIS

3. Pathophysiology: literature

• activated (renal) RAS as initial step leading to nephrosclerosis in obstruction
  – suppression of intrarenal RAS prevents formation of TGF-β, other factors and fibrosis
    • Shin GT et al. Kidney Int. 2005
    • Ishidoya S et al. Kidney Int. 1995
    • Berka JL et al. J Hypertens. 1994
    • Pimentel JL Jr et al. Kidney Int. 1995
TTT in HYDRONEPHROSIS

3. Pathophysiology: literature

Gobet, 1999:

Pressure within pelvis ↑

GFR ↓ and FF ↓

= delayed TTT
TTT in HYDRONEPHROSIS

4. Conclusions

• Clinical utility
  – Kidneys with timely TTT
    • not at risk
      – Clinical study: 67 out of 70
      – Animal experimental study: 12 out of 12
    • not at risk, even in the presence of an obstructive RFS
      – Clinical study: 9 out of 9
      – Animal experimental study: 3 out of 3
TTT in HYDRONEPHROSIS

4. Conclusions

• Clinical utility
  – Kidneys with delayed TTT
    • improve after therapy
      – Clinical study: 8 out of 10
    • lose function without therapy
      – Clinical study: 2 out of 3
      – Animal experimental study: 18 out of 18
TTT in HYDRONEPHROSIS

4. Conclusions

• Pathophysiology:

A delayed tissue tracer transit (TTT) is equivalent to a reduced filtration fraction and an activated renin-angiotensin system (RAS) resulting in an initially reversible, but finally irreversible functional compromise due to histomorphologic restructuring.
TTT in HYDRONEPHROSIOS

5. Outlook

Similar, prospective clinical and animal experimental studys with *quantitative analysis of TTT* are necessary to improve acceptance of TTT as a parameter for diagnostics and research.
Perspectives for future research: Diseases with FF compromise

• A. (Obstruction)
• B. (Renovascular disease)
• C. Post transplant ATN
• D. Post TPL rejection episodes
• E. Contrast material nephropathy
• F. Lupus nephritis
• G. Acute glomerulonephritis
• H. Post traumatic acute renal failure
• I. Afro-American athletes
• J. Acute drug induced renal compromise (animal studies)
  a. Assess FF in drugs which cause renal function to fall
  b. Little knowledge about cause of renal function loss when drug combinations are prescribed