Measurement of differential renal function and GFR with MR imaging

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MR evaluation of filtration function

• Two methods are available:
  – methods of clearance of a Gd-chelate:
    • based on blood samples
    • based on sequential imaging
  – methods based on dynamic imaging of the kidney:
    • differential renal function
    • single-kidney GFR
MR evaluation of filtration function

- MR glomerular agents for filtration:
  - Low molecular weight Gd-chelates (DTPA, DOTA…)
  
<table>
<thead>
<tr>
<th>Name</th>
<th>Brand name</th>
<th>Ligand</th>
<th>Structure</th>
<th>Ionicity</th>
<th>Osmolarity (mOsm/kg)</th>
<th>Viscosity 37°C (mPa s)</th>
<th>T1 relaxivity in blood, 1.5 T (L/mmol s)</th>
<th>T2 relaxivity in blood, 1.5 T (L/mmol s)</th>
<th>Renal excretion (T1/2; h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadopentetate</td>
<td>Magnevist</td>
<td>DTPA</td>
<td>Linear</td>
<td>Ionic</td>
<td>1960</td>
<td>2.9</td>
<td>4.3</td>
<td>4.4</td>
<td>1.6</td>
</tr>
<tr>
<td>Gadoterate</td>
<td>Dotarem</td>
<td>DOTA</td>
<td>Macrocyclic</td>
<td>Ionic</td>
<td>1330</td>
<td>2.0</td>
<td>4.2</td>
<td>6.7</td>
<td>1.6</td>
</tr>
<tr>
<td>Gadodiamide</td>
<td>Omniscan</td>
<td>DTPA-BMA</td>
<td>Linear</td>
<td>Nonionic</td>
<td>789</td>
<td>1.4</td>
<td>4.6</td>
<td>6.9</td>
<td>1.3</td>
</tr>
<tr>
<td>Gadoteranol</td>
<td>ProHance</td>
<td>HP-DO3A</td>
<td>Linear</td>
<td>Nonionic</td>
<td>630</td>
<td>1.3</td>
<td>4.4</td>
<td>5.5</td>
<td>1.6</td>
</tr>
<tr>
<td>Gadoveratamide</td>
<td>OptiMARK</td>
<td>DTPA-BMEA</td>
<td>Linear</td>
<td>Nonionic</td>
<td>1110</td>
<td>2.0</td>
<td>5.2</td>
<td>6.0</td>
<td>1.7</td>
</tr>
<tr>
<td>Gadobutrol</td>
<td>Gadovist</td>
<td>BT-DO3A</td>
<td>Macrocyclic</td>
<td>Nonionic</td>
<td>1390</td>
<td>4.9</td>
<td>5.3</td>
<td>5.4</td>
<td>1.5</td>
</tr>
</tbody>
</table>

- Same pharmacokinetics than iodine CM and 99mTc-DTPA:
  - freely diffusing within the extracellular fluid volume until equilibrium
  - elimination by glomerular filtration wo secretion or reabsorption
  - 20% extracted at the first pass
Method of plasma clearance

• **Sampling method:**
  Measurement of plasmatic and urinary Gd concentration by NMR spectrometry (10 MHz)

\[
GFR = \frac{U \times V}{P}
\]

- Hyperdiuresis
- 3 blood and urinary samplings

Choyke, Kidney Int 1992
Method of plasma clearance

- Sequential imaging method
Method of plasma clearance

- **Sequential imaging method:**
  - Coronal T1w MR images for 80 min
  - Injection of Gd: 0.05μmol/kg
  - ROI on liver, spleen and renal cortex

- **Model:**
  \[ GFR = a_2 \times ECFV \]
  - \( a_2 \): time constant of the second exponential phase
  - \( ECFV = 0.02154 \times W^{0.6469} \times H^{0.7238} \)

- **Patients:**
  - 13 volunteers with normal function

- **Reference:**
  - Iopromide plasma clearance

*Boss A. et al, Radiology 2007*
Method of plasma clearance

Optimal time for exponential curve fitting: 40-65 min

Mean difference: 5.9 ml/min ± 14.6

Boss A. et al, Radiology 2007
Dynamic MR imaging of the kidneys
Relationship MR SI - [Gd]

- Requirements +++ :
  - heavily T1 weighed sequence
  - small dose of Gd

Choyke, Radiology, 1989
Linear relationship SI - [Gd]

- **Impact on sequences:**
  - Strong T1 weighting:
    - GE sequence:
      - Short TR/TE, large FA for contrast dynamic range (90°)
  - Magnetization-prepared GE sequence (TFE)
    - saturation: 90°-120°
    - inversion (180°)
    - non-selective +++ for inflow effects in vessels
    - FA can be small for temporal resolution: 10-20°

- **Impact on the contrast agent:**
  - Need to decrease the T2* effects of Gd chelates:
    - decrease doses: half (0.05 mmol/kg) to fourth (0.025 mmol/kg) ? no consensus
    - hydration?
Differential renal function: $AUC$

$$RF = AUC \ (mm^2) \times KSurf \ (mm^2)$$

Spearman correlation
$$r = 0.92 \ p < .001$$

Rohrschneider, Radiology 2002
17 yo man, with UPJ syndrome fMRI after indwelling catheter

Differential renal function: \textit{AUC}

RK : 72%

LK : 28%
Differential renal function: Rutland-Patlak method

Arterial input function

Renograms

Patlak plots

68%

32%
Wendy, 7 yo 
Suspicion of duplication

A multicentric study (17 centres) is accomplished in France in 367 patients with unilateral obstruction, compared with scintigraphy (Coor. M. Claudon, Nancy)
Requirement for movement correction
Accuracy of functional volumes

Correlation between MR-derived morphological parameters and SK-GFR (35 pts, 59 k)

3D : Parenchymal volume

- normal vessel/insignificant RAS ($n=26; r=0.86, P<0.001$)
- significant RAS ($n=33; r=0.76, P<0.001$)

3D : Cortical volume

- normal vessel/insignificant RAS ($n=26; r=0.83, P<0.001$)
- significant RAS ($n=33; r=0.57, P<0.001$)
Correlation volume-DRF

Relationship between volume of functioning renal parenchyma and slope of the Rutland-Patlak plot in 307 kidneys.

Grattan-Smith, Ped Radiol 2008
Riccabona M, Radiology 2005
Correlation length-volume

renal length

Coulam, JMRI 2002

Bekker, Radiology 1999

Van den Dool, Radiology 2005
Measurement of SKGFR

- **Significance and clinical interest**:
  - GFR is used as an index of functioning renal mass: sum of filtration rates in each functioning nephron
  - Much better marker of functional status of the kidneys:
    - being the earliest and only clinical sign of renal disease
    - allowing serial monitoring to follow the course of kidney diseases

- **Because changes of GFR are inhomogeneous**:
  - Single kidney GFR
  - Local GFR
MR measurement of SKGFR

- **Based on dynamic Gd-enhanced T1w sequences**

- **Requirements**:
  - rapid T1w 3D sequence
  - conversion of SI into [Gd]
  - movement correction
  - cortical segmentation for modeling
  - renal volume calculation
  - application of a tracer kinetic model

- **Acquisition plane**:
  Longitudinal (coronal oblique) including kidneys in their long axis
  - important for AIF (aorta)
  - important for movements correction
Temporal constraints

- Temporal resolution
  - at least 4 seconds (better 1-2s)
- Length of acquisition:
  - 3 min for GFR
  - 10-15 min for excretion

**TABLE 1. Cutoff Values for the Required Temporal Resolution and the Acquisition Time**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DE &gt; 10%</th>
<th>TE &gt; 10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PV (mL/100 g tissue)</td>
<td>TR &gt; 9 s</td>
<td>AT &lt; 85 s</td>
</tr>
<tr>
<td>PF (mL/min/100g tissue)</td>
<td>TR &gt; 4 s</td>
<td>AT &lt; 35 s</td>
</tr>
<tr>
<td>TV (mL/100 g tissue)</td>
<td>TR &gt; 9 s</td>
<td>AT &lt; 255 s</td>
</tr>
<tr>
<td>TF (mL/min/100 g tissue)</td>
<td>TR &gt; 5 s</td>
<td>AT &lt; 230 s</td>
</tr>
</tbody>
</table>

This table demonstrates the thresholds beyond which the DE and the TE are larger than 10%.

Michaely HJ et al, Invest Radiol 2008
Optimal contrast dose

- Injected doses of Gd-DTPA above approximately 1.5 to 2 mmol do not result in increased precision of GFR.
- The highest GFR precision is achieved at approximately 0.02 mmol/kg dose in normal patients, and approximately 0.025 mmol/kg in patients with decreased renal function.

Ruzinek H et al, MRM 2001
Movement correction: impact on GFR

Total kidney:
- No motion correction
- Motion correction

Cortex:
- No motion correction
- Motion correction

GFR and GFR uncertainty for both motion correction and no motion correction.

Graphs showing the variation and reduction of GFR with patient numbers.
Segmentation of renal compartments

Vivier PH et al, in press

semiautomated segmentation technique based on the graph-cuts
Conversion of SI into concentration

• **Theory**: 

\[ [\text{Gd}] = \frac{(R_1 - R_{10})}{r} \]

where \( R_{10} \) is the bulk R1 relaxation rate of the tissue without Gd and \( r \) is the R1 relaxivity of the contrast agent within the tissue.

• **Methods**: 

  - phantom of tubes filled with Gd solutions at various concentrations:
    - relaxivity is not equivalent in solution and in tissues
  - equation driven by the sequence used
Rutland-Patlak method

• Optimal time controversial:
  – 40-110 s
  – 30-90 s
Compartment models

Two compartments model
(St Lawrence-Lee) = EF x RBF
Measurement of SKGFR

- **Modelization of one central slice**: 
  - GFR = mean slice GFR \times \text{cortical volume}

- **Modelization of all slices**: 
  - Addition of GFR from each voxel of each section 
  - Providing an intrarenal spatial distribution of GFR
Impact of the size of AIF

Cutajar et al, Eur J Radiol 2009
Reproducibility of GRF measurement

Fifteen healthy volunteers underwent two DCE-MRI studies under similar physiological conditions, 5 to 69 days apart (median 13 days)

Cutajar et al, Eur J Radiol 2009
Tracer kinetic renal models

Baumann-Rudin model
inflow-only model (filtration coefficient)

Patlak-Rutland model
based on a 2 compartment model;
outflow from tubules is ignored

Two-compartment model
outflow from tubules is taken into account
Annet et al. Lermoye et al.

Three-compartment model
outflow from tubules is taken into account
Lee et al.

From Bokacheva et al, MR Clin N Am 2008
MR measurement of SKGFR

- **Clinical series:**
  - Hackstein et al, JMRI 2003
  - Hackstein et al, JMRI 2005
  - Buckley, JMRI 2006
  - personal unpublished data

- **Heterogeneity of protocols**
  - Sequence (type and parameters)
  - Acquisition plane
  - Number of slices
  - Dose of contrast agent
  - Conversion from SI to [Gd]
  - Post-processing: ROI, movements, segmentation
  - Models
SK-GFR with Patlak-Rutland method

• Patients (n=28)
  – Reference: plasma clearance of iopromide
  – 15 ml Gd diluted in 60 ml infused in 60s
  – ROI including cortex + medulla on axial sections
  – MR-GFR vs reference using Rutland-Patlak plot:
    best correlation for 40-110s Pearson’s r = 0.86, SD 14.8 ml/min

Hackstein et al, JMRI 2003
Hackstein N, JMRI 2005
SK-GFR : PR vs two compartment model

• Patients with ARVD (n=39)
  – 75 kidneys
  – Reference: 51Cr-EDTA + 99mTc-DTPA
  – ROI including cortex + medulla on central slice

• MR-GFR vs NM-GFR:
  – Patlak-Rutland:
    Spearman’s $\rho = 0.81$, $p < .0001$
  – Compartmental model:
    Spearman’s $\rho = 0.71$, $p < .0001$

Overestimation by:
- 30% for PR method
- 100% for 2 Cpt model

Buckley, JMRI 2006
SK-GFR : P-R vs two compartment model

Two-compartment model that accounts for tubular outflow and the spread of the bolus in the renal vasculature

- **Sequence** :
  - saturation-prepared GE
  - single axial slice
  - 1.13 s/im
  - GD half-dose
- **Goldstandard**: 51Cr-EDTA
- **Model**:
  - cortical compartment model
    - ROI on cortex : r=0.82
  - Rutland-Patlak model:
    - ROI on cortex : r = 0.74
    - ROI on cortex + medulla : r = 0.63

Annet et al, JMRI 2004
MR measurement of SK-GFR

Patients (n=10)
- 20 kidneys
- Reference: 99mTc-DTPA renography + clearance

Method:
- 3D FLASH coronal, 3s/slab
- 4 ml Gd
- ROI including cortex and medulla separately

Results:
- Spearman’s $r = 0.84$ – $p < 0.001$
- Average difference: 11.9 ml/min
  (95%CI, 5.8-17.9 ml/min)
Conclusions

• MR imaging has a huge potential for:
  – Providing reliable data on differential renal function associated with morphological information
  – Providing reliable parenchymal volume calculations

• More time will be necessary for:
  – Providing reliable quantification of SKGFR….