Functional MR urography in children

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Résumé
Uro-IRM fonctionnelle chez l’enfant
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Abstract
MR Urography (MRU) provides both morphologic and functional information without radiation exposure. It enables the assessment of split renal function, excretion, and quantification of obstruction. MRU is thus complementary to ultrasonography in the assessment of pre- and post-natal obstructive uropathies in children. If available, MRU should be definitely preferred to intravenous urography.


The good spatial resolution and the excellent contrast enhancement of functional MR-urography provide high quality images for morphological studies. The good temporal resolution in optimised sequences can be used for kinetic analysis of contrast medium uptake in the kidney and gadolinium excretion in the renal cavities. Many authors (1–8) have found a good correlation between functional MR urography and renal scintigraphy with $^{99m}$Tc-MAG3 or $^{99m}$Tc-DTPA.

In our experience, the most routine indication for MR urography in children is hydronephrosis or uni/bilateral hydro-ureteronephrosis. Hydronephrosis involves a pyelocalyceal dilatation, but it is not always associated with urinary obstruction. The definition of obstruction used by most authors is that of Koff (9): a pathology preventing the flow of urine and which causes deterioration in renal function (or more specifically in the glomerular filtration rate) if it is not treated. This shows that the consequences of dilatation are difficult to predict. Indeed, most prenatal hydronephroses resolve spontaneously in the first years of life without affecting renal function. Therefore, surgery should be avoided in children with non-obstructive hydronephrosis. On the other hand, in case of obstruction, intervention, often surgical, must occur before renal function is affected. Thus the aim of functional MR urography for hydronephrosis is twofold: determine the relative (or differential) renal function and identify any obstruction. It is also the procedure of choice for anatomo-functional exploration of ureteral duplications because of the limited spatial resolution of scintigraphy and of the difficulty of differentiating the upper from the lower poles of the duplicated kidney (10).

Indications

In our experience, the most routine indication for MR urography in children is hydronephrosis or uni/bilateral hydro-ureteronephrosis. Hydronephrosis involves a pyelocalyceal dilatation, but it is not always associated with urinary obstruction. The definition of obstruction used by most authors is that of Koff (9): a pathology preventing the flow of urine and which causes deterioration in renal function (or more specifically in the glomerular filtration rate) if it is not treated. This shows that the consequences of dilatation are difficult to predict. Indeed, most prenatal hydronephroses resolve spontaneously in the first years of life without affecting renal function. Therefore, surgery should be avoided in children with non-obstructive hydronephrosis. On the other hand, in case of obstruction, intervention, often surgical, must occur before renal function is affected. Thus the aim of functional MR urography for hydronephrosis is twofold: determine the relative (or differential) renal function and identify any obstruction.

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Technique
Preparing the patient

Oral hydration one hour before the procedure is necessary. If possible the child should empty his/her bladder as much as possible, before then being catheterized by a professional. A cathlon is better than a butterfly needle to obtain the best flow rate for the gadolinium bolus. A 3 way stopcock is placed near the cathlon, with no extension tube to avoid any empty space and possible incomplete draining after the injection of forsemide and gadolinium. On the other hand to guarantee easy positioning in the MRI device, a long tube should attach the stopcock to the infusion. Sedation adapted to the child’s age and according to the local protocol is highly recommended (11) to avoid motion artefacts from crying or agitation. Until the age of 6, giving the child a bottle just before placing him/her in the device is usually enough. The child must be restrained and appropriate measures must be taken to monitor vital signs if the child is sedated.

Injections of furosemide and gadolinium chelates

The child is then placed in the MRI device. Furosemide is injected intravenously at a dose of 1 mg/kg in babies, and 0.5 mg/kg in children and young adults with a maximum dose of 20mg if renal function is normal. The injection of furosemide immediately before the gadolinium, called

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the F0 method (12) is now the most usual technique. This injection technique is based on that used in scintigraphy. It avoids the "dilution effect" (false impression of emptying of dilated cavities due to sudden dilution) and improves sensitivity for the diagnosis of obstruction in case of a pyeloureteral junction syndrome by distending the renal pelvis and increasing the size of the obstacle. It also improves emptying in case of simple stasis. On the other hand the risk of dehydration and cochlear toxicity from furosemide requires careful appropriate hydration during the procedure.

A half dose (0.05 mmol/kg), or even a quarter dose of gadolinium chelate (8, 13) is manually injected after the dynamic gradient-echo sequences have begun and pulsed with 15ml of isotonic solution. In young babies, the use of half doses is preferable because of the risk of a low signal-to-noise ratio, as a result of the difficulty in managing the low injected doses. The goal of these low doses is to obtain weak concentrations of gadolinium in the renal parenchyma, and thus minimize the T2 effect (reduction in signal intensity occurs with high gadolinium concentrations). Moreover, in this case, the relationship between gadolinium concentrations and the signal is relatively linear (14), allowing a functional analysis. Furosemide also mimics the T2 effect.

Recommendations on the use of gadolinium contrast media in pediatrics and the risk of nephrogenic systemic fibrosis (NSF) have been published (15). The key points to these recommendations concern prevention:

- MRI should only be performed if there is a formal indication;
- identify patients who are at risk of NSF: patients with renal insufficiency and liver graft patients. Ideally creatinine levels should be dosed and renal clearance should be calculated (table I) before performing MRI;
- carefully consider the indication for gadolinium injection. If clearance is below 60 mL/min, the injection should be reconsidered. If clearance is below 30mL/min, the indication should be discussed with a nephrologist. In both cases, patients and their parents should be informed of the risk and only macrocyclic gadolinium chelates should be injected.

Moreover, recent recommendations of the European Society of Urogenital Radiology (ESUR) (16) mention the renal immaturity of children less than a year old, which explains why the risk of developing NSF is higher in these patients. It is logically recommended to use Gadolinium-DPTA "with care". On the other hand, Dotarem®, which has a high affinity constant, can be used as long as basic precautions are taken. The injected dose of gadolinium should be as low as possible, without ever being more than 0.3 mmol/kg.

Sequences

A multi-channel coil should be used if possible. In children, breathing motion in the kidney is minimal, which means that free-breathing-acquisition is possible. Scout images of the entire abdomen should be made on all 3 planes. Then coronal oblique 2D or 3D, T2 heavily weighted images are acquired with fat saturation, parallel to the long axis of the kidneys (identified by localizing sagittal slices), covering the kidneys and extending to the pubis at a thickness of at least 40mm. This is a balanced FFE (Fast Field Echo) type sequence (17), or if this is not possible a rapid spin-echo sequence (HASTE or RARE) (18). Thin 3D heavily T2 -weighted slices may be useful for analysing implantation of an ectopic ureterocoele. The sagittal plane seems better than others in this case, because it results in fewer artefacts (fig. 1).

Then a T1 dynamic rapid gradient-echo sequence such as an FFE (Fast Field Echo) is begun. A coronal oblique image corresponding to the main axes of both kidneys is acquired. This can be a single slice (thickness = 1cm, temporal resolution=1 second), or multislice (3D dynamic sequence, called 4D, thickness 4 to 10mm, 3 to 30 slices, temporal resolution 3 to 8 sec). 4D sequences can be used to study the kinetics of enhancement of the entire parenchyma of both kidneys, but are more sensitive to blurring from motion from a child crying or breathing. The rectangular field of view should be adapted to the morphology of the patient and include all of both kidneys. For rapidity sake, Fourier plane acquisition is partial and the acquisition matrix should be small, for example 116x192. Each image is acquired in approximately 1 second (a 3D acquisition covering both kidneys should not reasonably last more than 2 or 3 seconds). The images are obtained continuously, according to the temporal resolution of the sequence for 5 minutes, then every 30 seconds for 10 to 15 minutes. If the latter images have

**Table I**

<table>
<thead>
<tr>
<th>Biological estimations of glomerular function from creatinemia.</th>
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<tbody>
<tr>
<td><strong>Adults</strong></td>
</tr>
<tr>
<td>Cockcroft-Gault formula</td>
</tr>
<tr>
<td>DFG=(140-age (in years))xweight (in kg)xk/[creat (in μmol/L)]</td>
</tr>
<tr>
<td>k=1.04 in women</td>
</tr>
<tr>
<td>k=1.25 in men</td>
</tr>
<tr>
<td>MDRD* (Modification of Diet in Renal Disease) formula</td>
</tr>
<tr>
<td>DFG=170x[creat (in mg/dL)]0.994x[age]0.173x[uremia (in mg/dL)]0.17x[Alb (in g/dL)]0.385xk</td>
</tr>
<tr>
<td>k=0.762 in women</td>
</tr>
<tr>
<td>k=1 in men</td>
</tr>
<tr>
<td>k=1.180 in black subjects</td>
</tr>
<tr>
<td><strong>Children</strong></td>
</tr>
<tr>
<td>Schwartz formula</td>
</tr>
<tr>
<td>DFG=kxheight (in cm)xk/creat (in μmol/L)</td>
</tr>
<tr>
<td>k=29 between 2-3kg for both sexes</td>
</tr>
<tr>
<td>k=35 between 3-12kg for both sexes</td>
</tr>
<tr>
<td>k=49 in boys between 12-42kg</td>
</tr>
<tr>
<td>k=49 in girls&gt;12kg</td>
</tr>
<tr>
<td>k=53 in boys&gt;42kg</td>
</tr>
<tr>
<td><strong>Conversion factors</strong></td>
</tr>
<tr>
<td>creatininemia: μmol/L &gt;0.0113=mg/dL et mg/dL≥88.5=μmol/L</td>
</tr>
<tr>
<td>uremia: mmol/L=6x[creat (in mg/dL)]-0.176</td>
</tr>
<tr>
<td>albuminemia: g/L=0.167=mmol/L</td>
</tr>
</tbody>
</table>

*Creat: creatininemia. Alb: albuminemia.*
artifact, they can be done again immediately. Acquisition begins before the injection to adjust the signal from the kidneys later on and to trace dynamic curves with a baseline of 0.

After the dynamic sequence, the same dose of gadolinium can be injected again to perform coronal and axial 2D or 3D T1 gradient-echo sequences 60 to 90 seconds later (parenchymal time) with fat saturation. Slices should be less than 5mm thick to avoid having partial volume effects deteriorate the precision of volume images. More homogeneous enhancement of the renal parenchyma than in the neighboring organs allows segmentation of the kidneys during semi-automatic post-processing of images. Two orthogonal planes can be used to search for cortical scarring.

In case of junction syndrome or renal artery stenosis, a gradient-echo 3D T1 angi-MRI sequence can be performed before the volume images, to identify the polar artery or locate the stenosis. If angi-MRI is performed, gadolinium must be injected again. The total dose of gadolinium including prior injections should not be more than 0.2mmol/kg (or 0.4mL/kg semi-molar gadolinium). In this case the volume images are immediately obtained after angi-MRI to take advantage of the injection.

It is not always necessary to search for a polar artery in cases of junction syndrome, this depends on the type of intervention planned by the surgeon, and the usual protocol. The inferior polar arteries are rarely the cause of pyeloureteral obstruction, and are usually a simple anatomical variant, with no pathological effect (19). If the planned surgical technique is retrograde endopyelotomy, the surgeon should be aware of the presence of a lower polar artery so that the incision at the pyelo-ureteral junction can be made with great care to avoid damaging the artery. Often when a polar artery is present another technique is used. Good communication with the surgeon, and a specific request to look for a polar artery should be obtained to limit the amount of gadolinium injected to the absolute minimum. Figure 2 shows the steps to an examination.

**Morphological evaluation**

An oblique coronal heavily T2-weighted sequence (fig. 3) provides a urographic image, showing hyperintense fluid-containing structures. The renal cavities and the entire length of the ureters can be rapidly studied in this slice. The bladder may also be evaluated, but not necessarily completely in the volume studied.

Thin 3D T2-weighted, CISS-type slices can precisely locate the orifice of an ectopic ureterocele (fig. 1) of an ectopic ureter.

**Functional evaluation**

Dynamic sequences can be used to study relative renal function and renal excretion. The functional analysis requires image processing software. We use Image J and the plug in of uroMRI that we have developed (14, 20, 21). They can be downloaded free of charge with the instruction manual on the NIH site National Institutes of Health.
Relative renal function

This is the contribution of each kidney (in percentage) to total glomerular function. This study is derived from $^{99m}$Tc-DTPA or $^{99m}$Tc-MAG3 scintigraphy and was adapted to MRI by Rohrschneider (4-7). Two values are required for each kidney: renal volume and the area under a segment of the curve. Renal volume is calculated by placing a region of interest (ROI) on the renal parenchyma, excluding the renal cavities. This is then repeated on all the slices (fig. 4). The volume is then determined by adding the selected voxels. The kinetics of contrast uptake in the renal parenchyma can be represented by a curve of signal intensity as a function of time called a renogram. This is obtained by manually drawing an ROI on the renal parenchyma, excluding the renal cavities, which is then automatically reproduced on all the slices in the dynamic sequence. Normally, the renogram begins by a vascular peak (fig. 5) corresponding to the arrival of the gadolinium bolus in the renal arterioles. The lowest point after this peak is "base level P," and the signal intensity increases more gradually after that. The beginning of this segment corresponds to the glomerular filtration of gadolinium. The end part of this segment is marked by the glomerular peak (G) which corresponds to the point of equilibrium between glomerular filtration and excretion. Gadolinium excretion then becomes predominant in the cavities which explains the gradual reduction in the signal after the G peak.

Because of the heterogenous magnetic fields and the asymmetric signals inherent in the use of multiple coils, only the relative signal should be studied. This is why the dynamic sequence should begin before the contrast medium arrives in the kidneys.

The area under the curve between point P and peak G is calculated for each kidney and represents the average glomerular activity of each parenchymal voxel. If there are artefacts the G peak is not always easy to identify. In this case, the 2 renograms should be studied separately (right and left). If the G peak is clear on one of the 2 renograms, the corresponding point should also be chosen for the other renogram (fig. 6). The time intervals must always be the same for the areas under the curve. The areas are then weighted according to the number of voxels (parenchymal volume) in each kidney. The software determines the relative renal function by compiling kidney volume and the area under the curve (21). An asymmetric renal function is defined as a difference of more than 10% between the 2 kidneys. (resulting in one kidney with a $<45\%$ function and the other $>55\%$ (22, 23). In cases of ureteral duplication, the relative renal function is broken down into the relative glomerular functions of the upper and lower poles (fig. 6). Longitudinal monitoring of relative renal function is especially useful, because obstruction is defined as the alteration in renal function over time. In case of bilateral hydronephrosis, the functional evaluation should obviously not only take into account the relative percentage of the 2 kidneys.

Excretion

Excretion is studied by placing an ROI on the parenchyma and the renal cavities on one image of the dynamic sequence. As mentioned above, the ROI is then automatically reproduced on all the images of the dynamic sequence. A excretion renogram is obtained, making it possible to determine if there is obstruction or not. O’Reilly’s scintigraphic classification (24) has been adapted to the F+0 protocol, classified into 3 groups: normal, obstruction, equivocal excretion (fig. 7). When there is no obstruction, the injection of furosemide causes the gadolinium stagnating in the dilated pyelocalyceal cavities to drain into the ureter by increasing the glomerular filtration rate. On the other hand, if there is obstruction, the furosemide has no effect and the gadolinium accumulates in the cavities.

Care must be taken when interpreting excretion renograms because the patient’s hydration, the relative renal function, the volume of the renal cavities, the decubitus, and the degree of vesicular filling are parameters that significantly modify
**Fig. 4:** Parenchymal renal segmentation for volume measurement.

Treatment of the 5 first images passing by the kidneys.

- **a** Non-segmented image.
- **b** Segmentation of the right kidney.
- **c** Segmentation of the left kidney.

**Fig. 5:** Renal parenchyma ROI parenchymal renogram.

V: vascular peak; P: P level; G: glomerular peak, A: area under the curve necessary for the relative renal function, between points P and G corresponding to glomerular filtration.
these results. No method exists to normalize or correct all of these parameters. (25–29). A normal excretion renogram confirms the absence of obstruction. On the other hand, it is difficult to definitely confirm obstruction even if the results of an excretion renogram do suggest obstruction. Indeed, Amarante studied children with hydronephrosis without obstruction (stable relative renal function over time) and reported that 44% of these patients had a renogram suggesting obstruction (25). The evaluation of obstruction cannot be done without first knowing the relative renal function over time. Indeed, stability of the relative renal function over time confirms the absence of obstruction (9). No morphological element can be used to differentiate dilatation with stasis from actual obstruction.

Obstruction can also be evaluated by Mean Transit Time (MTT) defined as the delay between the appearance of gadolinium in the renal parenchyma, and its appearance at the beginning of the ureter, but none of the parameters mentioned above are included in this case. Jones (2) calculated the relative renal function.

Fig. 6: Calculation of relative renal function in a case of left ureteral duplication in a 3 year old boy.

- **a** Renal scintigraphy with DMSA. Only the right-left ratio can be evaluated. The spatial resolution does not differentiate the upper from the lower pole of the left kidney.
- **b** Region of interest placed on the upper pole and the corresponding parenchymal renogram.
- **c** Segmentation of the upper pole of the left kidney; volume of 24 mL.
- **d** Region of interest placed on the lower pole and the corresponding parenchymal renogram. Segmentation of the inferior pole of the left kidney; volume of 35mL.

Relative renal function of the upper left pole is \( \frac{7107 \times 24}{(7107 \times 24) + (10486 \times 35)} \times 100 = 32\% \). The relative renal function of the lower left pole is 68%.
defined 3 categories in children in relation to the MTT: normal excretion (<246s), equivocal excretion (246-490s), and obstruction (>490s).

**MR urography of the future**

**Multi-compartment models**

In the past few years, multi-compartment models that were first applied to scintigraphy have been adapted to CT scan (30) then MRI (31) to study relative or even absolute renal function (glomerular filtration rate in ml/min). Although the determination of relative renal function is reliable in these models, this is not the case for absolute renal function. Indeed, studies in nuclear medicine have proven that clearance calculated by the Cockcroft method is more reliable than that determined by the compartment models in scintigraphy alone (that is without blood or urinary samples) (32).

For the moment the use of these models is still experimental. Nevertheless, they will probably play an important role in the near future. The Rutland-Patlak method is more extensively studied. Its primary application was to study cerebral perfusion (33, 34). It was then adapted to determine renal function in scintigraphy (35) and in tomodensitometry (30, 36, 37) then finally in MRI (31). The principles of the Rutland-Patlak method are described below. Most often, two compartments are individualized: a vascular compartment and a nephronic compartment. Several hypotheses must be accepted:
• the concentration of gadolinium is the same in the aorta and the renal arteries;
• the hematocrit is identical in the aorta and the renal vessels (this ignores the Fahraeus effect);
• the interstitial space is negligible (this is false in case of pyelonephritis or acute obstruction);
• signal variations in a voxel are proportional to concentration variations of gadolinium. This linear relationship can be approached with low doses of gadolinium and optimized sequences;
• the relationship between the signal and the gadolinium concentration is identical in both compartments. The quantity of gadolinium arriving in the aorta over time is called the “arterial input function”.

To measure this, an ROI is placed on the aorta during the dynamic sequence resulting in a curve (fig. 8). The integral under the curve at a time t corresponds to the quantity of gadolinium that is circulating in the aorta at time t.

A second ROI is placed on the renal parenchyma in the same way, excluding the cavities. The information obtained from these two ROI’s is used to determine the relative (or even absolute) renal function. The quantity of gadolinium, \( Q_{\text{Gd}} \), in a voxel corresponds to:

\[
Q_{\text{Gd}} = \Delta S \times p \times V_{\text{vox}}
\]

where \( \Delta S \) is the intensity of the measured signal – intensity of the signal without injection; \( p \) is the factor of proportionality between the signal and the concentration; \( V_{\text{vox}} \) is the voxel volume.

The factor of proportionality \( p \) which can be used to convert the signal into concentration (\( \Delta S \times p \)), cannot be taken into account because in the Rutland-Patlak equation, this factor is divided by itself.

The quantity of gadolinium in the kidney at a moment \( t \), \( R(t) \) corresponds to the sum of the quantities of gadolinium in the renal vascular space, \( V(t) \) and in the nephronic space, \( N(t) \)

\[
R(t) = V(t) + N(t)
\]

Since our hypothesis states that the concentration of gadolinium is identical in the aorta and the renal arteries:

\[
V(t) = v.Ao(t)\int_0^t Ao(t) dt
\]

\( v \) is the renal vascular volume; \( Ao(t) \) is the gadolinium concentration in the aorta at a time \( t \).

Because renal clearance \( \alpha \), is proportional to the quantity of gadolinium arriving in the aorta:

\[
\alpha \sim R(t) = V(t) + N(t)
\]

And by combining the preceding equations we obtain:

\[
R(t) = v.Ao(t) + \left( \alpha \int_0^t Ao(t) dt \right)
\]

The Rutland-Patlak equation is obtained by dividing this last equation by \( Ao(t) \):

\[
R(t) = \frac{v.Ao(t)}{Ao(t)} + \left( \alpha \int_0^t \frac{Ao(t) dt}{Ao(t)} \right)
\]

If all of the preceding hypotheses above are considered to be true, this equation corresponds to that of a line segment:

\[
y = b + ax
\]
b: the intrarenal vascular volume corresponds to the intersection of the segment with the ordinal axis in ml.
a: the slope of the segment $\alpha$ is proportional to renal clearance (renal clearance is obtained after correction by the hematocrit) in mL/s.

In fact the correction in relation to the hematocrit must be made to $\alpha$. Indeed, the signal measured in an aortic voxel corresponds to the variation in concentrations in the blood, but this variation can only be attributed to variations in plasma concentrations.

Renal clearance of the studied kidney (mL/min) (mL/min) = $\alpha \times (1 - \text{Hematocrit}) \times k$

$k$: constant

The relative renal function is calculated in the following manner:

Right relative renal function (%) = $\alpha_{\text{right}} / (\alpha_{\text{right}} + (\alpha_{\text{left}}) \times 100$

Dynamic 3D sequences

Three dimension T1 dynamic gradient-echo sequences which have been available (called 4D: 3D + time) for several years on MRI 1.5 Tesla, can be used to study the kinetics of enhancement for both kidneys. Theoretically this is a major advantage compared to single slice dynamic sequences, because enhancement kinetics of the entire kidney (by adding together all the renal voxels) can be studied. Nevertheless, to maintain acceptable temporal resolution, for now, 4D sequences have a weaker spatial resolution than single slice sequences. This could limit the study of an atrophied parenchyma in children. Moreover for the moment there is no software available for routine use to study enhancement kinetics in the kidneys on multiple slices.

Conclusion

MR urography is already the reference procedure for the anatomofunctional investigation of ureteral duplications in children. It will also most certainly replace $^{99m}$Tc-MAG3 or $^{99m}$Tc-DTPA scintigraphy in the evaluation of urinary obstruction in the near future, because there is no ionic radiation involved and because a morphological examination can be completed in less than 40 minutes. However, the difficulties of this technique should not be underestimated, first when working with children (approach, sedation, restraint) and also because of the complexity of post-processing of images.

References

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