Simultaneous evaluation of renal morphology and function in live kidney donors using dynamic magnetic resonance imaging

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Abstract

Background. Evaluation of potential kidney donors requires the assessment of both kidney anatomy and function. In this prospective study, we sought to expand the diagnostic yield of magnetic resonance (MR) by adding functional measurements of glomerular filtration rate (GFR) and split renal function.

Methods. Between 2007 and 2009, all potential kidney donors presenting to our facility underwent a comprehensive single-stop MR study that included an assessment of anatomy, angiography and functional measurements. GFR was measured after a bolus injection of gadobutrol (4 ml, ∼0.05 mmol/kg) and calculated from the washout of the signal intensity obtained over the liver. Split renal function was calculated from the increase of signal intensity over the renal cortex. Values were compared to renal scintigraphy with ⁹⁹ᵐTc-DTPA from the same day.

Results. The MR investigation was successfully performed in 21 participants. The GFR derived from MR (MR-GFR) correlated well (r = 0.84) with the GFR derived from scintigraphy (DTPA-GFR). The mean value of the paired differences was 4 ± 13 [SD] ml/min/1.73 m² and was not significantly different from zero. The ratio between right and left kidney function was similar with both techniques (1.01 ± 0.17 with MR and 1.06 ± 0.12 with scintigraphy, P = 0.20).

Conclusions. We demonstrate an MR-based approach to comprehensively evaluate both kidney anatomy and function in a single investigation, thereby facilitating the evaluation of potential kidney donors.

Keywords: donor evaluation; GFR; kidney transplantation; MR; scintigraphy

Introduction

The evaluation of potential kidney donors requires the assessment of kidney morphology and vascularization, as well as kidney function as indicated by the glomerular filtration rate (GFR) [1,2]. Currently, the anatomy of the kidneys is analysed using abdominal ultrasound or CT scans, whereas assessment of the renal vasculature is mainly performed non-invasively using computer tomography (CT) or magnetic resonance (MR) angiography [3,4]. Measurement of the GFR requires separate studies. The best GFR values are obtained from single-shot plasma disappearance curves after the injection of a filtration marker and repeated, timed blood sample collections. Creatinine clearance is less accurate and subject to collection error.
In addition, the use of formulas such as the MDRD or the Cockcroft–Gault formula is not suitable [2,5]. Knowledge of the exact GFR value and the contribution of each kidney to the overall GFR are essential in the evaluation of potential kidney donors, particularly given the increasing age of donors [6]. According to the guidelines of the British Transplantation Society [2], the acceptable minimum GFR value for a donor under 40 years old is 86 ml/min/1.73 m² and this value decreases to 50 ml/min/1.73 m² for donors 80 years of age. Therefore, potential kidney donors are recommended to undergo GFR measurements, preferably with radioisotopes combined with renal scintigraphy, to obtain information about split renal function.

Using dynamic MR imaging techniques, measurements of GFR and split renal function have become feasible [7–9]. This is based on the fact that gadolinium (Gd)-containing contrast media are exclusively excreted by glomerular filtration [10,11] and thus may serve as filtration markers [12]. In a previous study, our group demonstrated the feasibility and accuracy of determining the GFR value after bolus injection of gadobutrol in healthy volunteers with normal renal function [13]. The aim of this study was to expand the diagnostic yield of MR by adding functional measurements for GFR and split renal function during routine MR studies of potential kidney donors.

Materials and methods

Subjects

From June 2007 through March 2009, all potential kidney donors presenting to the collaborative transplantation centre of the University of Tübingen were consecutively enrolled in this study. The study was approved by the local ethics committee and registered at the European Union Drug Regulating Authorities Clinical Trials (EudraCT, number 2007-001090-28). The study was in accordance with the revised ethical standards of the Helsinki Declaration of 1975. During the evaluation procedure, all potential kidney donors at our centre are routinely scheduled to receive MR examination of the kidney including MR angiography and renal scintigraphy. In the context of the study, the MR examination was extended to functional measurements. All participants gave written informed consent to extended MR examination and scientific evaluation of the results.

**MR protocol**

MR examinations were performed on two 1.5 T units (Magnetom Avanto [Unit A] and Magnetom Sonata [Unit B], Siemens Medical Solutions, Erlangen, Germany). Anterior and posterior flexible, six-channel phased-array body coils were applied over the kidneys for signal reception, whereas a built-in body coil was used for spin excitation.

After the acquisition of a series of T1-weighted, gradient-echo localizer images, T2-weighted half-Fourier, single-shot fast spin echo images (TR/TE = 1110 ms/118 ms, fast spin echo factor of 77, section thickness = 5 mm) were recorded to provide anatomical orientation. To prevent motion artefacts, a navigator-gating technique was applied allowing image acquisition at nearly identical diaphragm position. Navigator-gated T1-weighted images were acquired up to 60–70 min after the injection of 4 ml of gadobutrol. In six patients, T1-weighted images were acquired using Unit A with a TurboFLASH sequence (TR/TE = 528 ms/1.15 ms, flip angle = 8°, TI = 300 ms, bandwidth = 600 Hz/Px, voxel size = 3.0 × 3.0 × 30 mm³). For the remaining 17 patients, T1-weighted images were acquired using a TrueFISP sequence with a centric-reordered k-space filling scheme (TR/TE = 527 ms/1.79 ms, flip angle = 70°, I = 300ms, bandwidth = 574 Hz/Px, voxel size = 3.0 × 3.0 × 30 mm³) using Unit B. A linear relationship between signal growth and the longitudinal relaxation rate was assumed for both sequences [14].

MR angiography was performed, after obtaining functional measurements, using a fat-saturated, T1-weighted 3D-FLASH sequence (TR/TE = 2.84 ms/0.91 ms, flip angle = 28°, bandwidth = 570 Hz/Px) with administration of another 11 ml of gadobutrol (corresponding to ~0.15 mmol/kg).

MR contrast media (gadobutrol, Gadovist®) was provided by Bayer Schering Pharma AG (Berlin, Germany), now Bayer Vital (Leverkusen, Germany). This investigator-initiated study was entirely organized and performed at our institution. None of the authors were employed by Schering.

**GFR determination using MR**

The MR-GFR was measured after a bolus injection of gadobutrol (4 ml, corresponding to ~0.05 mmol/kg) [13]. Signal intensity curves were recorded over 60–70 min as a function of the examination time, from regions-of-interest (ROIs) that were manually drawn over the liver (Figure 1A). In a pilot study, determination of the GFR using ROIs over the liver showed the best agreement to the reference method compared to ROIs over the renal cortex or spleen [13]. A linear relationship between the MR signal intensity and the concentration of the contrast medium in the tissue was previously proven for both sequences used in this study and for the amount of gadobutrol injected in the subjects [15]. The signal intensity curve, after the injection of the contrast medium, followed a typical bi-exponential pattern (Figure 1B) due to the distribution of gadobutrol from the vascular space into the extracellular fluid volume.
(ECFV) and the clearance of gadobutrol from the ECFV via glomerular filtration [10]. Thus, the reduction of the signal intensity in the tissue is a measure of renal function. The GFR was calculated from the decay constant of the second exponential phase α2 and the calculated ECFV, which are associated by the relationship [16]:

\[
\frac{\alpha_2}{ECFV} \rightarrow GFR = \alpha_2 \times ECFV
\]

α2 was obtained after linear regression from the logarithmic signal intensity curve between the 20th and 60th minute (Figure 1B).

The ECFV was calculated from the formula [17]:

\[
ECFV = 0.02154 \times W^{0.6489} \times P^{0.7236}
\]

where \(W\) indicates the body weight (in kilogrammes) and \(P\) is the body height (in centimetres).

Finally, the GFR values were normalized to a body surface area (BSA) of 1.73 m2.

**Determination of split renal function using MR**

Split renal function was assessed from signal intensity curves generated by ROIs drawn over the renal cortex [14]. The curve exhibits a pattern unique to the kidney [18] where a second peak occurs within the first minutes after injection. This pattern results from the enrichment of contrast media in the cortex due to glomerular filtration (Figure 1C).

The slope \(\beta\) of the linear increase of each kidney can be estimated by linear fitting of the logarithmic signal. The single renal function (SRF, in percentage) results from the product of the estimated slope and the area of the ROI drawn over the corresponding kidney, normalized to the sum of the products of both kidneys, as follows:

\[
SRF = \frac{\beta_\text{r} \times ROI_\text{r}}{\beta_\text{l} \times ROI_\text{l} + \beta_\text{r} \times ROI_\text{r}}
\]

where \(\beta\) is the slope estimated from the linear fit, ROI is the area of the region-of-interest and the subscripts r and l indicate right and left kidney, respectively.

**Scintigraphy**

On the same day as the MR examination, each subject underwent renal scintigraphy, which served as a reference method. Patients were placed on a gamma camera (Siemens Diacama®) in supine position and posterior dynamic images were acquired for up to 30 min. After a bolus injection of \(\sim 150\) MBq technetium-labelled diethylene-triamine-pentacetic acid (99mTc-DTPA), a known filtration marker [19], GFR values (in units of ml/min) were estimated from two blood samples taken 1 and 2 h post-injection using the following equation:

\[
GFR = \left[ \frac{D \times \ln(P_1/P_2)}{T_2-T_1} \exp \left( \frac{T_1 \ln P_1 - T_2 \ln P_2}{T_1-T_2} \right) \right]^{-0.979}
\]

where \(D\) indicates the dose in counts per minute, \(P_1\) the plasma activity at Time point 1 (in units of counts per millilitre) and \(P_2\) the plasma activity at Time point 2 (in units of counts per millilitre). Data was evaluated using commercially available software (Siemens Icon® 9.5 KB 34, MPE-programme: Renal_GFR, Rev. 3.3). GFR values were normalized to a BSA of 1.73 m2. Split renal function was estimated from ROI analyses using the dedicated tool in the MPE-programme.

**Laboratory evaluation**

On the day of MR and scintigraphy analyses, serum creatinine and creatinine clearance were determined, the latter from a fresh 24-h urine collection. Serum creatinine concentration was measured enzymatically on auto-analysers from Bayer (Leverkusen, Germany). Creatinine clearance values were normalized to a BSA of 1.73 m2. MDRD-GFR values were calculated according to the isotope dilution mass spectrometry-corrected, simplified MDRD formula [20].

| Table 1. Baseline characteristics of the study participants (n = 23) |
|-----------------|-----------------|
| Age             | 52 ± 13 years   |
| Gender distribution (male/female) | 39/61% (n = 9/n = 16) |
| BSA             | 1.86 ± 0.16 m²  |
| Systolic BP     | 118 ± 9 mmHg    |
| Diastolic BP    | 76 ± 6 mmHg     |
| Serum creatinine| 0.77 ± 0.16 mg/dl |
| 24-h creatinine clearance | 120 ± 30 ml/min/1.73 m² |
| Albuminuria     | 12 ± 6 mg/24 h  |

Arithmetic means ± SD. Blood pressure (BP) values were determined from 24-h ambulatory Holter measurements.

Based on \(n = 5\) subjects, not detectable in the remaining subjects.

**Results**

From June 2007 through March 2009, a total of 23 potential kidney donors presenting to the collaborative transplantation centre of the University of Tübingen were consecutively enrolled in this study. The baseline characteristics of the cohort are shown in Table 1. All subjects were healthy and were not taking any medications. In addition, they did not present any contraindications for MR.

**Anatomical evaluation**

T2- and T1-weighted MR images, acquired with both TurboFLASH and TrueFISP, allowed for the evaluation of kidney size and anatomy in all subjects. Normal kidney size was observed in all patients. T2-weighted images revealed the presence of renal cysts in three patients. With the exception of one patient with double ureter, all patients had single ureters on both sides. Contrast-enhanced MR angiography allowed for a comprehensive evaluation of the renal vascular status in all subjects. Accessory renal arteries were found in four patients, whereas three patients had double renal veins.

**Functional measurements—GFR and split renal function**

Measurements of MR-GFR were successfully performed in 21 participants, with technical failures occurring in two. The mean GFR was 112 ± 25 ml/min/1.73 m², as determined from scintigraphy, and 115 ± 22 ml/min/1.73 m², as determined from MR. As shown in Figure 2A, the GFR values showed good agreement with a correlation coefficient of \(r = 0.84\). The mean of the paired differences was 4 ± 13 ml/min/1.73 m² and was not significantly dif-
different from zero, excluding a bias between both methods (Figure 2B). Data obtained from TrueFISP \((n = 15)\) and TurboFLASH \((n = 6)\) sequences showed both good accordance with the scintigraphy results. The mean paired difference was slightly higher with TurboFLASH \((10 \pm 7 \text{ ml/min/1.73 m}^2)\) compared to TrueFISP \((1 \pm 15 \text{ ml/min/1.73 m}^2)\), whereas the correlation coefficient was slightly weaker with TrueFISP \((r = 0.82)\) compared to TurboFLASH \((r = 0.97)\).

The mean values for right and left kidney function were 51 \(\pm 3\) and 49 \(\pm 3\)%, respectively, as determined by scintigraphy, and 50 \(\pm 4\) and 50 \(\pm 4\)%, respectively, as determined by MR. When expressed as a ratio, the mean ratio between right and left kidney function was similar with both techniques \((1.06 \pm 0.12\) with scintigraphy and \(1.01 \pm 0.17\) with MR, \(P = 0.20)\). Both values were not significantly different from unity and the correlation coefficient was \(r = 0.46\). Again, there was no bias between both methods (Figure 2C and D).

**Correlation between MDRD-GFR and creatinine clearance**

The mean MDRD-GFR was significantly lower than the mean DTPA-GFR \((96 \pm 26 \text{ vs } 112 \pm 25 \text{ ml/min/1.73 m}^2,\) respectively). The mean paired difference was \(-16 \pm 27 \text{ ml/min/1.73 m}^2\) and significantly different from zero \((P = 0.01)\) Thus, MDRD-GFR underestimated the true GFR systematically. The correlation coefficient was \(r = 0.44\) (Figure 3). In contrast, mean creatinine clearance \((118 \pm 30 \text{ ml/min/1.73 m}^2)\) did not significantly differ from the value obtained by DTPA-GFR and the mean paired difference was \(6 \pm 28 \text{ ml/min/1.73 m}^2\), a value

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**Fig. 2.** (A) Plot of the GFR values obtained by MR-GFR and DPTA-GFR (correlation coefficient of \(r = 0.84\); dashed line represents the line of identity); (B) Bland–Altman plot excluding a systematic bias between MR-GFR and DPTA-GFR (the solid line indicates the mean of the paired differences; dotted lines represent \(\pm 2\) SD); (C) plot of the ratio between right and left kidney function obtained by MR-GFR and DPTA-GFR (the correlation coefficient was \(r = 0.46\); dashed line represents the line of identity); (D) Bland–Altman plot excluding a systematic bias between MR-GFR and DPTA-GFR (the solid line indicates the mean of the paired differences; dotted lines represent \(\pm 2\) SD).
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Discussion

In this study, we demonstrate the feasibility and accuracy of a MR-based approach to comprehensively evaluate both kidney anatomy and function of potential kidney donors in a single investigation. Compared to the reference method, DTPA scintigraphy allowed us to obtain similar values for absolute GFR and split renal function without a systematic bias between both methods. These results confirmed our preliminary findings [21]. In a similar study, an MR-based approach to assess both kidney anatomy and function was evaluated in donors [22]. However, absolute quantification of GFR was only possible using a conversion factor obtained from radioisotope clearance. Our group previously established the feasibility and accuracy of determining GFR and split renal function using MR in healthy volunteers [13]. These functional measurements have been presently translated into a clinical setting, rendering this protocol an attractive option for the evaluation of potential kidney donors in a comprehensive single-stop investigation which represents a potential alternative to the three diagnostic modalities currently in use (i.e. renal scintigraphy, ultrasound and renal arteriograms). Besides the potential reduction in health care costs, our protocol diminishes the organizational burden for the medical staff and the high time demand for potential donors.

To date, determination of GFR using dynamic MR techniques relied on the measurement of single kidney GFR by acquisition of a signal in the renal cortex within minutes after the injection of contrast medium [7,8]. Our protocol, in contrast, measures whole-body GFR from the washout of signal intensity over the liver, enabling us to calculate the decay constant, \( \alpha \), which is also measured using plasma clearance methods. The course of the signal intensity over the renal cortex is used only to estimate split renal function. This approach leads to a relatively long acquisition time of 60–70 min, which might cause discomfort in some patients. Prior to the MR study, all participants were informed about the acquisition time and the possibility to abort; however, none of the participants withdrew prematurely from the study. Despite the long acquisition time, the MR study is still assumed to be time- and cost-effective, since both anatomical and functional measurements are accomplished in a single-stop investigation with post-processing and data analysis lasting <1 h. Hence, the MR-GFR could be determined in a total evaluation time of <4 h. In contrast to the above-mentioned protocols, post-processing was less elaborate as, e.g. labour-intensive three-dimensional segmentation was not required [7,8]. Technical failure occurred in two patients due to motion artefacts during MR, which might limit a broader adoption of this method in some patients.

Although providing excellent anatomical information of the kidney, the pitfalls of an MR-based approach may lie in the visualization of renal vessels. Whereas many studies have found good agreement between MR angiography and CT angiography [23] or digital subtraction angiography [24] and surgical findings [25], a few studies have reported a reduced sensitivity of MR angiography in identifying accessory renal arteries when compared to CT angiography [26,27]. In our studies, vascularization of all explanted kidneys was in agreement with the MR findings.

Measurement of GFR and split renal function is strongly recommended in potential kidney donors [2]. The British Transplantation Society has published minimum GFR values that are predictive of the safety of the loss of renal mass for the donor during his or her lifetime. The minimum acceptable GFR is 86 ml/min/1.73 m² for a donor under 40 years old and decreases to 77, 68, 59 and 50 ml/min/1.73 m² for ages 50, 60, 70 and 80, respectively. The basis for such a detailed decision algorithm is an accurate measurement of GFR using filtration markers such as inulin, radioisotopes or using MR, as shown in this study. Given the broad range of GFR values in our cohort (73 to 157 ml/min/1.73 m²) and the relatively high donor age (52 ± 13 years), an exact GFR measurement is clearly warranted. The use of creatinine-based formulas or creatinine clearance cannot be an accurate alternative, as is confirmed in our study. The MDRD-GFR systematically underestimated the DTPA-GFR and showed a weak correlation, which is in agreement with the poor performance of the MDRD formula in patients with normal GFR [28]. In contrast, creatinine clearance did not significantly differ from DTPA-GFR, yet the correlation was also weak. Both MDRD-GFR and creatinine clearance showed great variation and resulted in substantial over- and underestimation of DTPA-GFR in individual patients (Figure 3).

Saturation recovery navigator-gated TrueFISP has recently been proven to result in a higher signal yield compared to the TurboFLASH sequence [15]. The TurboFLASH sequence is extremely T1-weighted, whereas a TrueFISP sequence has a combined T1- and T2-weighting. In this study, renal function was evaluated using both TrueFISP and TurboFLASH sequences resulting in comparable results. Both sequences proved to be robust and to provide consistent GFR values. If at all, TurboFLASH had a ten-
dency to overestimate GFR slightly (mean difference 10 ± 7 ml/min/1.73 m²) compared to TrueFISP (1 ± 15 ml/min/1.73 m²). The total amount of applied Gd-containing contrast medium was 15 ml gadobutrol, corresponding to ~0.2 mmol/kg, which did not exceed the recommended maximum dose for MR angiography (0.3 mmol/kg). The development of nephrogenic systemic fibrosis, which has been related to Gd-containing contrast media, can be excluded at this dose and in patients with normal renal function.

Conclusion

In summary, we demonstrate an MR-based approach to comprehensively evaluate both kidney anatomy and function in a single investigation, facilitating the evaluation of potential kidney donors.

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Conflict of interest statement. None declared.

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