Morphologic and Functional Magnetic Resonance Imaging of Renal Artery Stenosis: A Multireader Tricenter Study

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Abstract. The effect of combined morphologic and functional magnetic resonance (MR) imaging on the interobserver and intermodality variability for the grading of renal artery stenosis is assessed. In a randomized, blinded tricenter analysis, seven readers evaluated 43 renal arteries on x-ray digital subtraction angiography (DSA), 3D-Gadolinium MR angiography (3D-Gd-MRA), cine phase-contrast flow measurement (PC-flow), and a combined analysis of the last two. Interobserver variability was assessed for the grading of renal artery stenosis as well as regional vessel visibility. Intermodality variability for stenosis grading was analyzed in cases in which the readers agreed on the degree of stenosis in DSA. DSA had a substantial interobserver variability for the grading of stenosis (mean κ = 0.64). 3D-Gd-MRA revealed a slightly improved interobserver variability but incorrectly graded 6 of 34 stenoses on a two-point scale (<50%, ≥50%). The combined approach of 3D-Gd-MRA and PC-flow revealed the best (P = 0.0003) interobserver variability (median κ = 0.75) and almost perfect intermodality agreement with DSA (97% of cases). These findings were confirmed in a prospective analysis of 97 renal arteries. The vessel visibility of the renal artery ostium was significantly better in 3D-Gd-MRA than in DSA, whereas the visibility of the hilar and intrarenal vessels was significantly worse (P = 0.0001). A combined morphologic and functional MR examination significantly reduces interobserver variability and offers reliable and reproducible grading of renal artery stenosis based on stenosis morphology and hemodynamic changes. It can be considered a safe and noninvasive alternative for diagnostic DSA in cases that do not require assessment of intrarenal vessels.

It is currently of debate whether x-ray digital subtraction angiography (DSA) still can be considered the gold standard for the diagnosis of renal artery stenosis. Although the technique has a high spatial resolution, pitfalls in stenosis grading can arise from the overlay of atherosclerotic plaques or tortuous vessels, as the technique is limited to a few two-dimensional projections. In addition, the cost of this procedure is high, usually exceeding $2000 US. Particular problems arise in patients with impaired renal function in whom the administration of nephrotoxic contrast agents might lead to permanent renal failure.

Magnetic resonance angiography is noninvasive and the gadolinium chelate contrast agents used are not nephrotoxic when administered in the recommended doses. The recently introduced three-dimensional gadolinium enhanced magnetic resonance angiography (3D-Gd-MRA) technique acquires renal artery contrast angiograms in a single breath-hold without the typical artifacts of in-plane saturation or intravoxel dephasing (1). In the current literature, high accuracies have been reported for grading of renal artery stenosis compared to x-ray DSA (2–6). However, fundamental differences between these two techniques affect the comparability of the data. As a result, the overall acceptance of 3D-Gd-MRA is still limited. With 3D-Gd-MRA, only a spatial resolution of approximately 1.5 mm³ usually can be achieved on standard clinical scanners, allowing a simplified four-scale grading scheme for renal artery stenosis. It represents a truly three-dimensional data set, which can be reformatted and viewed in multiple orientations.

A major advantage of MR imaging is that not only morphologic data of the arteries can be acquired but also functional information of blood flow and perfusion. As a result, different techniques have been advocated to assess the hemodynamic and functional significance of renal artery stenosis. These techniques identify changes in blood flow, flow pattern, renal tissue perfusion, or excretory function (7–10). Detection of a significant high-grade stenosis is thereby not limited to the exact morphologic determination of the true reduction of the vascular diameter. High accuracies have been reported with these techniques for detection of hemodynamically or functionally significant stenoses (11–13). In particular, the analysis
of the renal flow profile from cardiac-gated phase-contrast MR flow measurements helps to identify stenotic kidneys, in which the autoregulatory capacity is exceeded (14). These techniques provide a functional assessment, but they do not adequately map the arterial anatomy for planning of surgical revascularization. The aim of this study, therefore, was to assess whether a combined morphologic and functional MR assessment of renal artery stenosis in a single MR examination reduces discrepancies in stenosis interpretation and improves the overall accuracy for detection of high-grade stenoses. In a tricenter multireader analysis, the diagnostic value of 3D-Gd-MRA in combination with cine phase-contrast flow measurements (PC-flow) was compared to DSA findings in terms of interobserver and intermodality variability.

Materials and Methods

Study Concept

In a multireader analysis, seven readers retrospectively evaluated a total of 43 renal arteries on DSA, 3D-Gd-MRA, PC-flow, and a combination of the last two. The patients were imaged at three different institutions. On the basis of the results of the multireader analysis, a total of 97 renal arteries were prospectively graded on 3D-Gd-MRA and PC-flow measurements by three readers.

Patients

Retrospective Multireader Analysis. Between December 1996 and May 1997, a total of 23 patients with atherosclerotic renal artery stenosis (10 men, 13 women; age range, 46 to 76 yr; average, 59 yr) were evaluated at the German Cancer Research Center (Heidelberg, Germany; 12 patients), the University of Michigan (Ann Arbor, MI; 10 patients) or the Ann Arbor Veteran Affairs Medical Center (1 patient). Twenty patients had bilateral renal arteries; 3 patients initially presented after a single nephrectomy. In all patients, 3D-Gd-MRA, cine phase-contrast (Cine-PC) flow measurements, and DSA were performed in diagnostic quality. The study was approved by the institutional review board, and informed consent was obtained.

Prospective Evaluation. To assess prospectively the value of a combined morphologic and functional stenosis grading, we examined a total of 60 patients (39 men, 21 women; age range, 30 to 81 yr; average, 47 yr) in a single center (German Cancer Research Center) using a combined exam of 3D-Gd-MRA and Cine-PC-flow measurements. Any patient referred to our department because of an abnormal BP indicating possible renal artery stenosis (high diastolic value, recent onset with rapid deterioration) or a positive finding on Doppler ultrasound was included. As these patients were successively acquired, the group contained both normal individuals without renal artery stenosis and patients with various degrees of renal artery stenosis. Because in the current clinical practice 3D-Gd-MRA often is considered the definitive diagnostic test, DSA was not available for most cases and therefore is not included in further data analysis.

Methods

MR imaging was performed on three high-performance clinical 1.5 T MR systems: either a Magnetom Vision (Siemens, Erlangen, Germany; maximum gradient strength, 25 mT/m; shortest rise time to maximum, 300 μs) or two Signa Echospeed (General Electric, Milwaukee, WI; maximum gradient strength, 22 mT/m; shortest rise time to maximum, 180 μs). On the Magnetom Vision, a four-element phased-array coil was used, whereas on the Signa Echospeed scanner, the built-in body coil was used. All three sites strictly adhered to the following imaging protocol.

Localization of Renal Arteries. The aorta and the kidneys were localized with sagittal T1-weighted gradient echo sequences performed in a single breath-hold. These images were used for the positioning of the 3D-Gd-MRA slab.

3D-Gd-MRA. For breath-hold contrast-enhanced MR angiography, fast 3D gradient echo sequences were used (Magnetom Vision: TR = 5 ms, TE = 2 ms, bandwidth = 488 Hz/pixel; Signa Echospeed: TR = 4.7 to 6.1 ms, TE = 1.1 to 1.4 ms, bandwidth = 31.2 kHz). An 8- to 10-cm-thick volume was aligned with the anterior margin of the infrarenal aorta covering posteriorly as much of the kidneys as possible. A rectangular 24- to 30-cm × 30- to 40-cm field of view was used. With 44 to 56 slices and 128 to 180 phase-encoding steps, a nearly isotropic spatial resolution of approximately 1.5 × 1.8 × 1.8 mm could be achieved. This resulted in a scan time between 26 and 40 s.

For synchronization between acquisition of the k-space center and contrast media infusion, either a testbolus technique (Magnetom Vision) or an automated detection of contrast media arrival (Smartprep, Signa Echospeed) was used as described previously (15). Gadolinium-DTPA (Berlex Laboratories, Wayne, NJ) was administered at a dose of 0.2 mmol/kg body wt and an infusion rate of 3 ml/s using either an automated infusion system (CAI 626; Dolton, Uster, Switzerland) or hand injection with a standardized tubing set (Smartset; Topspins, Ann Arbor, MI).

Cine-PC-Flow Measurements. Cine-PC-flow measurements were performed with cardiac gating using either prospective (Magnetom Vision) or retrospective (Signa Echospeed) gating. As previously described (11), the scan plane was set up perpendicular to the renal artery approximately 1 cm distal to the ostium (field of view, 22 cm; slice thickness, 6 mm; matrix, 256 × 256). In stenosed arteries, the plane was prescribed 1 to 2 cm distal to the stenosis. For the Magnetom Vision system, a PISP (fast imaging with steady state precession) sequence was used (TR = 13 ms, TE = 6 ms, velocity-encoding = ±75 cm/s). For each time frame, a flow-sensitive and a flow-compensated scan was obtained resulting in a minimum temporal resolution of 2 x TR = 26 ms. To acquire a 256 × 256 matrix for each time frame, a total measurement time of approximately 3 to 4 min was required. On the Signa Echospeed system, a retrospectively gated gradient echo sequence (TR = 18 ms, TE = 5 ms, velocity encoding = ±70 cm/s) with bipolar opposed gradients was used for flow encoding. The number of reconstructed time frames was chosen to result in a temporal resolution between 25 and 32 ms. To avoid errors in the PC-flow curve as a result of undersampling, we set the maximum number of time frames to 32. Because the spatial resolution of the flow measurements only allowed reliable display of vessels with a diameter of 2 to 3 mm, the measurements were limited to the main renal arteries.

The phase-contrast data were analyzed off-line on a workstation as described previously (11,16). In brief, a region of interest was manually drawn along the margins of the vessel cross section. Velocity time curves were calculated from the flow data in each time frame after applying a correction for phase noise and aliasing. Each data point on the curve thus represents the mean velocity averaged over the vessel area for that time frame.

DSA. DSA was performed on standard angiography equipment (Polydiagnost DVI-II/Integris DF 3000, Philips Medical Systems, Shelton, CT, or Multistar, Siemens Medical Systems, Iselin, NJ). A transfemorally inserted 5-F pigtail catheter was positioned with the side holes at the level of the suspected renal artery origins between the first and second lumbar vertebrae. Anteroposterior DSA was per-
formed with injection of 20 to 36 ml of contrast media (Imagopaque 300 or Omnipaque 300; Nycomed, Wayne, PA) at a rate of 15 to 18 ml/s. Additional oblique views were obtained in an angle of 18° to 25°. In case of a distal stenosis, the renal artery was also selectively catheterized with a 5-F double curve or Cobra catheter, with injection of an additional 9 to 10 ml of contrast media at a flow rate of 5 to 6 ml/s.

**Data Preparation**

The data preparation for the reading was carried out by a single radiologist, who did not participate in the multireader analysis and was blinded to the clinical history as well as the DSA and the 3D-Gd-MRA readings. The 3D-Gd-MRA images were reformatted using the satellite workstation. For each renal artery, targeted maximum intensity projection images were obtained at multiple angles. Each case was filmed on a different sheet of film without the patient’s name, name of institution, or imaging parameters. Each kidney was labeled with a random number. The DSA images for each patient were also filmed without any identifying parameters and were also labeled with a random number.

The Cine-PC-flow curves were scaled to a maximum velocity of 35 to 40 cm/s (velocity averaged over the vessel area) and plotted separately for each renal artery using the same system for randomization.

**Image Analysis**

**Retrospective Multireader Analysis.** The data were analyzed by a total of seven readers: three radiologists from the University of Michigan and Ann Arbor Veteran Affairs Medical Center, three radiologists from the German Cancer Research Center, and one vascular surgeon. The 3D-Gd-MRA and DSA images as well as the PC-flow curves were randomized and shown to the readers in the order of randomization. In addition, a combination of 3D-Gd-MRA images and the corresponding PC-flow curves for each renal artery were presented to the reader in randomized order. To avoid bias as a result of fatigue toward the end of the reading, we also randomized the

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**Figure 1.** Cine phase-contrast flow curves for different degrees of renal artery stenosis. A semiquantitative grading scheme is applied on the basis of distinct changes in the waveform pattern. This scheme was shown to the readers as a guideline for the grading of hemodynamic changes. Note that the absolute scaling is the same for all four flow curves. Normal flow profiles (A) reveal a characteristic early systolic peak and a midsystolic maximum. Low-grade stenoses (B) typically reveal only a partial loss of the early systolic peak (solid arrow). Moderate stenoses (C) demonstrate an almost complete loss of the early systolic peak and a decrease of the midsystolic maximum (open arrow). High-grade stenoses (D) have a featureless flattened flow profile.
order of the presentation of the four different imaging modalities (MRA, DSA, PC-flow, combined analysis) for each reader. All readers were blinded to the clinical data of the patients as well as the interpretations of other readers.

Image analysis included grading of the degree of stenosis as well as assessment of vessel visibility. Stenosis grading in the MRA and DSA images was based on reduction in vessel diameter using a four-point ordinal scale: 0, no stenosis; 1, stenosis <50%; 2, stenosis ≥50%; 3, stenosis >80%. The maximal stenosis was defined as the ratio between the narrowest diameter within the stenosis and the diameter of the nearest normal segment of the main renal artery downstream. The readers were advised to confirm their grading based on visual impression by physically measuring the actual reduction of vessel diameter. In addition to the grading of renal artery stenosis in the main renal arteries, the presence and number of accessory renal arteries was noted. Because of the limited spatial resolution of 3D-Gd-MRA, any accessory renal artery stenosis was graded as either present or absent.

In accordance with previous studies, the PC-flow curves were graded on the basis of the severity of hemodynamic abnormalities represented by changes in the shape of the flow profile (11,13,14,17). These characteristic changes were initially identified in a preliminary patient study and later confirmed by invasive animal measurements (11,14). The presence or absence of the three distinct features of the PC-flow curve were noted, i.e., the early systolic velocity maximum (early systolic peak), the subsequent incision, and the lower second midsystolic peak (Figure 1A). Findings were consistent with either a normal curve (grade 0) or partial loss of the early systolic peak as an indicator of a hemodynamically nonsignificant low-grade stenosis (<50%, grade 1; Figure 1B). Almost complete or complete loss of the early systolic peak and decrease of the midsystolic peak indicated moderate stenosis (50%, grade 3; Figure 1C), and a featureless flattened flow profile with no systolic velocity components was representative of a high-grade stenosis (grade 4; Figure 1D). Figure 1 was available for the readers as guideline for the grading of the hemodynamic changes. Combined analysis was performed by integrating the morphologic information of 3D-Gd-MRA and the functional information of corresponding PC-flow curves for each renal artery. On the basis of the combination of the two modalities, the overall degree of stenosis was defined using the same grading scheme as above.

Vessel visibility was assessed on 3D-Gd-MRA and DSA images for the ostium of the renal artery as well as the proximal, distal, hilar, and intrarenal segments. A three-point ordinal scale was used: 1, not identified; 2, identified but poorly defined; 3, clearly defined with definite evaluation of patency.

Prospective Evaluation. On the basis of the results of the retrospective multireader analysis, the prospectively acquired 3D-Gd-MRA and PC-flow data of 97 renal arteries was read and graded by three blinded readers in the same manner as described above. Interobserver variability among the three readers was assessed for the results of 3D-Gd-MRA alone as well as the combined analysis of 3D-Gd-MRA and PC-flow measurements. Grading was performed on a 2-point scale as noted above (<50%, ≥50% degree of stenosis).

Statistical Analyses

The data entry procedures and statistical analysis were carried out with the statistical software system SAS (SAS for Windows, version 6.12; SAS Institute, Cary, NC). For each of the four modalities (MRA, DSA, PC-flow, combined evaluation), the seven readers were compared with each other by means of a weighted κ test. Interval data arising from κ values and ordinal data of the vessel visibility and stenosis scores were analyzed using the Wilcoxon signed rank test.

Results

Retrospective Multireader Analysis

Interobserver variability for the seven readers is shown in Figure 2 for the different imaging modalities. Substantial differences are found in the distribution of the weighted κ values. For the DSA, a narrow range of κ is seen with values between 0.61 and 0.67 (25%, 75% quartile) and a median of 0.64. No substantial differences are present for the PC-flow curves. For 3D-Gd-MRA alone, the values are higher (25%, 75% quartile; 0.56 and 0.68).

Table 1. Interobserver agreement for the different imaging modalities

<table>
<thead>
<tr>
<th>Scale</th>
<th>DSA</th>
<th>Combined</th>
<th>MRA</th>
<th>Flow</th>
</tr>
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<tbody>
<tr>
<td>4-point scale (0%, &lt;50%, ≥50%, &gt;80%)</td>
<td>24/43</td>
<td>25/43</td>
<td>23/43</td>
<td>20/43</td>
</tr>
<tr>
<td>2-point scale (&lt;50%, ≥50%)</td>
<td>35/43</td>
<td>42/43</td>
<td>39/43</td>
<td>36/43</td>
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</tbody>
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* DSA, digital subtraction angiography; MRA, 3D-Gadolinium magnetic resonance angiography.
Table 2. Intermodality agreement

<table>
<thead>
<tr>
<th>Agreement</th>
<th>MRA/DSA</th>
<th>Combined/DSA</th>
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<tr>
<td>Agreement ≥6 readers</td>
<td></td>
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<tr>
<td>4-point scale</td>
<td>15/23</td>
<td>18/23</td>
</tr>
<tr>
<td>(0%, &lt;50%, ≥50%, &gt;80%)</td>
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</tr>
<tr>
<td>2-point scale</td>
<td>28/34</td>
<td>33/34</td>
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<tr>
<td>(&lt;50%, ≥50%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All arteries (mode score)</td>
<td>34/43</td>
<td>41/43</td>
</tr>
<tr>
<td>2-point scale</td>
<td></td>
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<td>(&lt;50%, ≥50%)</td>
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True degree of stenosis in DSA defined as agreement by 6 or more readers.

True degree of stenosis in DSA defined as mode score of all readers.

median, 0.63, 0.73, 0.7), although the distribution still substantially overlaps with that of DSA and PC-flow. The combined analysis of 3D-Gd-MRA and PC-flow shows substantially higher κ values than DSA; the 25% quartile only marginally overlaps with the 75% quartile of DSA (25%, 75% quartile; median, 0.67, 0.8, 0.75). The difference between the median of both distributions was found to be significant when analyzed by the Wilcoxon signed rank test (P = 0.0003).

For each of 43 renal arteries, the disagreement for the degree of stenosis was assessed by determining the difference between the maximum and minimum score estimates reported by the seven readers. In the combined analysis, agreement (difference between minimum and maximum score = 0) between the readers was found in a higher number of vessels than in DSA or 3D-Gd-MRA alone. In particular, maximum discrepancy between the readers was found in only one case for the combined evaluation, whereas 3D-Gd-MRA revealed four cases and DSA revealed six cases with the maximum difference in the stenosis scores. When analyzed by the Wilcoxon signed rank test, this difference was significant (P = 0.0038), whereas no significant difference was present between DSA and 3D-Gd-MRA alone.

Given the large number of readers, it was considered acceptable to call “agreement” in all cases in which at least six of the seven readers reported the same degree of stenosis on the ordinal scale (Table 1). On the original four-point scale (0 = 0%, 1 = ≤50%, 2 = >50%, 3 = >80%), agreement was found in a little more than half of the cases with no substantial differences between the modalities. In accordance with previous studies (11,18), the original scale was then reduced to a two-point scale of either nonsignificant (≤50%) or significant (>50%) disease. With these less restrictive criteria, agreement was found for the combined evaluation in all but one case; disagreement was present in three of these cases for 3D-Gd-MRA and in seven of these cases for DSA.

In the next step, the agreement between the modalities for the degree of stenosis was analyzed. The true degree of stenosis was considered the grade that had been reported in DSA with agreement of the readers either on a four-point scale (23 arteries) or on a two-point scale (32 arteries) (Table 2). On the two-point scale, all except one vessel were correctly graded by the combined analysis compared with DSA, whereas 3D-Gd-MRA did not agree with DSA in five of these cases. To compare the agreement between the modalities for all arteries, we used the mode of the scores reported by the seven readers in DSA as the true degree of stenosis for each vessel. The combined analysis revealed a substantially higher agreement than 3D-Gd-MRA alone (41 versus 34 correctly graded vessels). In particular, 3D-Gd-MRA tended to overgrade proximal moderate stenoses (Figure 3), miss proximal low-grade stenoses (Figure 4), and completely miss distal/hilar stenoses, even when they were moderate to high grade (Figure 5). In these cases, integrating the information from the hemodynamic changes in the PC-flow curves resulted in the correct up- or downgrading of the degree of stenosis in the combined analysis.

The number of accessory renal arteries detected on DSA varied highly among the seven readers, ranging from 2 to 9 with a mode value and a median of 6. Because these numbers were considered to be too few for further statistical analysis, the total agreement between MRA and DSA for the presence of either no accessory renal artery or one or more accessory renal arteries was assessed for each reader (Table 3). As can be seen from Table 3, the relative percentage of agreement between MRA and DSA was similar for all readers with a median of 82%. Overestimation of the number of accessory arteries was noted with similar frequency on both MRA and DSA. Overall, only two accessory renal artery stenoses were found, which was considered to be too few data for further analysis. One stenosis was consistently detected by all readers; the other was missed by five of the seven readers.

To analyze further the discrepancy between DSA and 3D-Gd-MRA, the visibility of the different vessel segments was compared (Table 4). For both modalities, all readers most commonly could clearly identify and evaluate the patency of the ostial, proximal, and distal segment of the renal artery. When the data of all readers and vessels were compared by means of a Wilcoxon signed rank test, the vessel visibility found in 3D-Gd-MRA for the vessel ostium was significantly higher than in DSA, whereas no significant differences were present for the proximal and distal part. For the hilar vessel segments, four of the seven readers most commonly could not identify the vessel at all in 3D-Gd-MRA, whereas maximum vessel visibility was still reported by all readers in DSA for this particular segment. This difference became more prominent for the intrarenal vessels. For both hilar and intrarenal vessel segments, significant differences in visibility between DSA and 3D-Gd-MRA were found in favor of DSA.

Prospective Analysis of 3D-Gd-MRA and Flow

In the prospective analysis of the 97 renal arteries on 3D-Gd-MRA, a total of 43 normal renal arteries were found (median; range, 42 to 48), 18 low-grade stenoses (median; range, 14 to 23), and 35 high-grade stenoses (median; range, 30 to 36). On 3D-Gd-MRA alone, only 58 of 97 renal arteries were graded identically by all three readers on a two-point
scale (<50%, ≥50%), whereas on the combined analysis, this was the case for 72 of 97 renal arteries. This increase in interobserver agreement was statistically significant (P < 0.01). The corresponding k values increased from 0.48 (median; range, 0.43 to 0.51) to 0.67 (median; range, 0.58 to 0.73). Figure 6 shows an example of a renal artery stenosis that was graded inconsistently by the three readers on 3D-Gd-MRA alone but graded identically in the combined analysis.

Discussion

The introduction of 3D-Gd-MRA has substantially increased the clinical impact of renal MRA because high-quality angiograms can be acquired noninvasively and without nephrotoxic contrast media. Despite these advantages, x-ray DSA still is considered the gold standard for determining the degree of renal artery stenosis for several reasons. First, the quality of 3D-Gd-MRA has been inconsistent and major improvements such as optimized bolus timing have only recently evolved. Second, the scanner performance is still not uniform at all sites, limiting spatial resolution or shortening acquisition time. The main shortcoming of 3D-Gd-MRA is spatial resolution. Although a spatial resolution of up to 1 mm³ already has been achieved, the decrease of signal to noise seems to make it impossible to achieve values as high as the 0.3 mm³ found in DSA (19). One strength of MRA, however, is the variety of information that can be obtained, including both morphologic and functional data. So the question is whether additional functional information about renal blood flow enhances the accuracy and consistency of renal artery stenosis grading.

These data in 43 arteries of 23 patients show that the combination of morphologic information of 3D-Gd-MRA with the functional information of PC-flow significantly improves the accuracy of the renal MRA examination. Furthermore, the combination produces a level of interobserver agreement that surpasses that obtained with x-ray DSA. The influence of interobserver variability, which affects both modalities, is an important problem in the clinical routine because multiple observers, including physicians from different fields, commonly interpret one study. Therefore, even in the gold standard DSA, the true degree of stenosis cannot be defined on the basis

Figure 3. (A) Digital subtraction angiography of a 59-year-old woman with right renal artery stenosis (arrow). The degree of stenosis was reported as moderate (50% to 80%, grade 2) with agreement of all readers. All readers agreed on a normal left renal artery. (B) 3D Gadolinium MR angiography (3D-Gd-MRA; TR = 5.2 ms, TE = 1.1 ms, flip angle = 45°, matrix = 128 × 256, field of view = 24 × 32 cm, 44 contiguous slices, acquisition time = 29 s) of the same patient. Because of the limited spatial resolution, the stenotic lumen of the right renal artery is not clearly identified (arrow), and all readers uniformly reported a too high degree of stenosis (grade 3, >80%). There was agreement with the DSA finding regarding the normal left renal artery. (C) The cine-phase contrast (Cine-PC) flow curve (TR = 18, TE = 5, temporal resolution per time frame = 34 ms) of the right renal artery reveals only moderate changes, in particular incomplete loss of the early systolic peak. The midsystolic velocity components are still preserved, although slightly decreased. In the combined analysis of the 3D-Gd-MRA and PC-flow curve, all readers downgraded the degree of stenosis to moderate (grade 2). The left renal artery reveals a completely normal flow profile with a preserved early systolic peak, which was read as grade 0 in good agreement with the normal vascular anatomy.
of a single observation (18). This fact has been neglected by several studies that have graded renal artery stenosis by 3D-Gd-MRA on a three- or four-point ordinal scale using DSA as the standard of reference.

In this study, this problem became obvious by the results of the multireader study. The standard of reference revealed the worst interobserver variability, and agreement of at least six readers was found in only 56% of the arteries. Even on a clinically applicable two-point grading scale, agreement was found in only 80%. In six cases, maximum disagreement was found, i.e., some readers reported a high-grade stenosis while others considered the vessel normal. The corresponding results for 3D-Gd-MRA were slightly better; however, this proved not to be significant. To ensure complete blinding and unbiased reading, we chose the seven readers as well as the patients from three different institutions. All data were kept completely anonymous, including measurement parameters, and were shown to each reader in a randomized order. To minimize the effects of the different data postprocessing steps on the interpretation of 3D-Gd-MRA, DSA, and PC-flow, we showed the readers data that had been postprocessed in a standardized manner. In the initial multireader analysis, only patients with renal artery stenosis had been included. To control for this selection bias, we carried out a second prospective study, in which 97 patients were successively enrolled regardless of whether a stenosis was present. The results were similar to those found in the retrospective study, with significant improvement of interobserver agreement on combined 3D-Gd-MRA and PC-flow analysis as compared with the sole angiographic evaluation alone (Figure 6).

The discrepancy of these results, which agree with other, similar studies (18), is related to the primary variable itself. Although in our institutions specific recommendations are given to physically measure the degree of stenosis rather rely on visual judgment, we find that the interpretation of the reduction in vessel diameter is subject to a high interobserver variability. It is also influenced by image degradation as a result of breathing artifacts, motion, poor bolus timing, or signal dephasing. Therefore, our study was designed to include a second functional MR modality that allows grading of the degree of stenosis independent from the reduction of vessel diameter. Cine-PC measurements look at the pattern of blood flow in the renal artery. As a stenosis develops, changes in vascular resistance alter the shape of the flow curve in characteristic ways that correlate with the degree of stenosis. This makes the technique particularly attractive because these hemodynamic changes can be ranked in categories, which allows functional grading of the stenosis on a semiquantitative scale analogous to the one used for morphologic grading. Through

Figure 4. (A) DSA of a 50-year old woman after bypass graft to the right kidney and nephrectomy on the left. A stenosis is found at the ostium of the bypass graft (arrow), which was reported as low grade (grade 1, ≤50%) by six of the seven readers and moderate (grade 2, >50%) by one reader. (B) On the corresponding 3D-Gd-MRA (TR = 5.2 ms, TE = 1.1 ms, flip angle = 45°, matrix = 128 × 256, field of view = 24 × 32 cm, 44 contiguous slices, acquisition time = 29 s), the stenosis is not seen. The graft was interpreted as normal by all readers. (C) The Cine-PC-flow measurement (TR = 18, TE = 5, temporal resolution per time frame = 24 ms) recorded in the bypass graft reveals a partial loss of the early systolic peak (arrow), whereas the incision and the midsystolic maximum are completely preserved. This finding is typical for a low-grade stenosis. In the combined 3D-Gd-MRA and PC-flow analysis, a grade 1 stenosis was reported by all readers.
The scaling of each PC-flow curve on an absolute range of velocity, the waveform changes could be analyzed in a standardized approach (Figure 1). Combining the morphologic data of 3D-Gd-MRA with the functional data of the PC-flow measurements proved to be highly reliable in the decision making. The interobserver variability was significantly better compared with DSA, and the overall agreement among all readers was significantly higher. On a two-point scale, agreement was achieved for 98% of all vessels.

The results also reveal a remaining discrepancy between 3D-Gd-MRA and DSA for the degree of stenosis, if this intermodality comparison is based on the true degree of stenosis defined as reader agreement in DSA (Figures 3 through 5). This disagreement is substantial on a four-point scale and is still present even on a two-point scale. In addition to the lower spatial resolution of 3D-Gd-MRA, this is related to the loss of vessel visibility in the more distal segments of the renal artery as a result of parenchymal enhancement and venous overlay (Figure 7). For the region of the bifurcation, renal hilus and intrarenal vessels, the visibility in DSA was significantly

Table 3. Percentage of agreement between MRA and DSA for the presence or absence of accessory renal arteries

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<thead>
<tr>
<th>Reader</th>
<th>Agreement between the Number of Accessory Renal Arteries Found</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DSA = MRA</td>
</tr>
<tr>
<td>1</td>
<td>79.5%</td>
</tr>
<tr>
<td>2</td>
<td>82.1%</td>
</tr>
<tr>
<td>3</td>
<td>82.1%</td>
</tr>
<tr>
<td>4</td>
<td>76.9%</td>
</tr>
<tr>
<td>5</td>
<td>84.2%</td>
</tr>
<tr>
<td>6</td>
<td>77.5%</td>
</tr>
<tr>
<td>7</td>
<td>87.8%</td>
</tr>
<tr>
<td>Median</td>
<td>82.1%</td>
</tr>
</tbody>
</table>

* Accessory renal arteries were graded as absent, single, or multiple.

The results also reveal a remaining discrepancy between 3D-Gd-MRA and DSA for the degree of stenosis, if this intermodality comparison is based on the true degree of stenosis defined as reader agreement in DSA (Figures 3 through 5). This disagreement is substantial on a four-point scale and is still present even on a two-point scale. In addition to the lower spatial resolution of 3D-Gd-MRA, this is related to the loss of vessel visibility in the more distal segments of the renal artery as a result of parenchymal enhancement and venous overlay (Figure 7). For the region of the bifurcation, renal hilus and intrarenal vessels, the visibility in DSA was significantly

TE = 1.3 ms, flip angle = 45°, matrix = 128 × 256, field of view = 24 × 32 cm, 44 contiguous slices, acquisition time = 34 s) reveals limited visibility of the bifurcation and the hilar vessels as a result of venous and parenchymal overlay (open arrow). None of the readers detected the stenosis at the bifurcation (solid arrow) even in this projection, which is similar to the DSA. Note the poor visibility of the lower segmental artery. (C) The Cine-PC-flow measurements (TR = 18, TE = 5, temporal resolution per time frame = 18 ms) demonstrate a complete loss of the early systolic peak as well as a slightly decreased mid-systolic maximum consistent with a moderate stenosis (grade 2). In the combined analysis, this data resulted in an upgrade of the stenosis to moderate by six readers and to low-grade by one reader. Note the similarities between this PC-flow curve and the one of the moderate right renal stenosis in Figure 4C scaled on the same absolute range of velocities.
higher than in 3D-Gd-MRA (Table 4). The low spatial resolution particularly influences the detection of accessory renal arteries (Table 3).

Conversely, DSA has various pitfalls as well. As a two-dimensional technique limited to a few projections, overlaying structures such as tortuous vessels or calcified plaques can mask the presence of a renal artery stenosis. Eccentric stenosis, which often occurs in atherosclerotic disease, can be falsely graded when viewed only en face rather than in various projection as on 3D-Gd-MRA. In addition, the position of the catheter in the aorta is crucial for optimum enhancement of the arteries of interest. Accessory renal arteries that arise unusually high or low from the aorta might not be displayed on an injection from a standard catheter position. This might also have contributed to the fact that the percentage of accessory renal arteries consistently identified both on 3D-Gd-MRA and DSA was only 80%. Distal renal artery stenoses often require selective catheterization for accurate grading, which, however, increases the frequency of complications from atherosclerotic emboli. These problems have led various authors to the conclusion that DSA can no longer be considered the gold standard for imaging of the renal arteries (20–22). 3D-Gd-MRA also is cheaper than DSA, with current cost of approximately $500 to $1000 US. Two limitations of 3D-Gd-MRA remain, such as obese patients who do not fit into the MR system and patients with implanted electronic devices such as cardiac pacemakers.

Regardless of whether 3D-Gd-MRA or DSA is used, the problem of the sole morphologic information remains, i.e., high interobserver variability as a result of simply carrying out a morphologic measurement of the vessel diameter. This measurement is limited by errors of projection such as from overlaying or torturous vessels. Therefore, the use of an additional MR modality for stenosis grading that does not depend on the exact visibility of each vessel segment should improve the overall detection and grading of stenosis. The combined analysis not only revealed almost perfect agreement between 3D-Gd-MRA and DSA on the two-point scale but also significantly reduced interobserver variability.

These results suggest several conclusions. Even for the gold standard, the true degree of stenosis is difficult to determine because this modality has substantial interobserver variability. In addition, DSA itself has limitations that call into question its current status as a gold standard for stenosis grading. The combination of a morphologic and functional MR modality significantly reduces interobserver variability and improves the accuracy of stenosis grading. We therefore propose the combined protocol of 3D-Gd-MRA and PC-flow measurements as a new noninvasive radiologic technique for reproducible and exact grading of renal artery stenosis.

There are two limitations to our study. First, the number of patients with DSA correlation was limited. This was related mainly to the availability of patients with renal DSA, because a substantial decrease in diagnostic DSA studies already had been present in our institutions since the introduction of 3D-Gd-MRA. However, it is a strength of the study that a large number of readers evaluated the cases in a highly standardized manner. Second, DSA was not available in the subgroup of patients evaluated prospectively. However, it needs to be pointed out that these patients were successively referred to 3D-Gd-MRA by the nephrologist, primary care physician, or vascular surgeon. As 3D-Gd-MRA is now considered reliable and robust, these patients only rarely undergo DSA today, mainly for reasons of preoperative evaluation of renovascular anatomy or direct angiographic intervention by transluminal angioplasty.

3D-Gd-MRA and PC-flow measurements are continuously evolving. Therefore, the reported values for spatial or temporal resolution may be exceeded by current state-of-the-art tech-

<table>
<thead>
<tr>
<th>Vessel Segments</th>
<th>Vessel Visibilitya (Mode Score)</th>
<th>Wilcoxon Signed Rank Test (P Values)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reader 1</td>
<td>Reader 2</td>
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<tr>
<td>-----------------</td>
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</tr>
<tr>
<td>DSA</td>
<td></td>
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</tr>
<tr>
<td>ostial</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>proximal</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>distal</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>hilar</td>
<td>3</td>
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</tr>
<tr>
<td>intrarenal</td>
<td>2</td>
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</tr>
<tr>
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<td>ostial</td>
<td>3</td>
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<tr>
<td>intrarenal</td>
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<td>1</td>
</tr>
</tbody>
</table>

*a Vessel visibility assessed by a score from 1 to 3 (1, not identified; 2, identified but poorly defined; 3, clearly defined with definite evaluation of patency).

*b Vessel visibility in DSA significantly better than in 3D-Gd-MRA.
niques (23). In particular, the spatial resolution of the PC sequences did not allow for measurements in small accessory renal arteries. During the study, however, we used the most advanced scanners available. In addition, the same scan parameters were achieved on MR systems from different vendors at different sites, making our conclusions highly transferable to the general application. It needs to be clarified that many older generation MR scanners, which are still not capable of performing the proposed protocol, are in use. However, in the next 5 yr, it can be expected that many of these older systems will be replaced because current high-performance MR scanners are now cheaper to maintain and more efficient in patient throughput, thus outweighing the cost of the investment. In terms of complexity of the scan setup, the proposed protocol can be performed by any trained MR technician, therefore making this technique highly reproducible.

In summary, 3D-Gd-MRA already provides slightly better interobserver variability than DSA but still suffers from limitations in spatial and temporal resolution. This particularly affects the accurate evaluation of distal renal artery stenoses. It is the adjunct of a second functional MR modality to 3D-Gd-MRA that significantly improves interobserver variability and further increases accuracy for stenosis grading. Because of the lack of radiation and nephrotoxic exposure, it should therefore be considered a replacement for diagnostic DSA in the majority of cases.

Other functional techniques also can be combined with 3D-Gd-MRA, which might further increase the amount of information obtained in a single MR examination. This techniques might be able not only to detect the presence of renal artery stenosis but also to quantify the amount of renal damage induced by the stenosis (24).

Figure 6. A 79-year-old woman with a right renal artery stenosis (arrow). (A) In the prospective assessment of 3D-Gd-MRA, this stenosis was differently graded by each of the three readers with the scores ranging from 1 (stenosis <50%) to 3 (stenosis >80%). This discrepancy among the readers is most likely related to the length of the stenosis with substantial fluctuations in vessel diameter. (B) In the combination of 3D-Gd-MRA and PC-flow measurements, all readers graded the degree of stenosis identically as grade 2 (stenosis ≥50%, <80%). The readers were able to identify the complete loss of the early systolic peak (arrow) with a partially preserved midsystolic maximum, making this stenosis a typical grade 2 lesion.
Acknowledgments
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References
11. Schoenberg SO, Knopp MV, Bock M, Kallinowski F, Just A, Essig M, Hawighorst H, Schad L, van Kaick G: Renal artery 3D-Gd-MRA (TR = 5 ms, TE = 2 ms, flip angle = 50°, matrix = 160 × 256, field of view = 27 × 36 cm, 44 contiguous slices, acquisition time = 35s). (C) The Cine-PC-flow curve (TR = 13 ms, TE = 6 ms, temporal resolution per time frame = 26 ms) reveals a featureless, completely flattened flow profile consistent with a high-grade stenosis. All readers interpreted these findings as grade 3 changes, and the degree of stenosis remained unchanged in the combined analysis.

**Figure 7.** (A) A 51-year-old man with hypertension. DSA reveals an eccentric proximal stenosis (solid arrow) of the right renal artery, which was read as high-grade stenosis (grade 3, >80%) by all readers. (B) All readers also reported a high-grade stenosis (solid arrow) on


