Correlation of Hemodynamic Impact and Morphologic Degree of Renal Artery Stenosis in a Canine Model

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Abstract. In a noninvasive comprehensive magnetic resonance (MR) examination, the morphologic degree of renal artery stenosis was correlated to corresponding changes in renal artery flow dynamics. Different degrees of stenosis were created with the use of a chronically implanted inflatable arterial cuff in seven dogs. For each degree of stenosis, an ultrafast three-dimensional gadolinium MR angiography with high spatial resolution was performed, followed by cardiac-gated MR flow measurements with high temporal resolution for determination of pulsatile flow profiles and mean flow. Flow was also measured by a chronically implanted flow probe. In three of the dogs, trans-stenotic pressure gradients (∆P) also were measured via implanted catheters. Five different degrees of stenosis could be differentiated in the MR angiograms (0%, 30%, 50%, 80%, >90%). The MR flow data agreed with the flow probe within ±20%. Stenoses between 30 and 80% gradually reduced the early systolic peak (Max 1) of the flow profile but only minimally affected the midsystolic peak (Max 2) or mean flow. Stenoses of more than 90% significantly depressed mean flow by more than 50%. The ratio between Max 1 and Max 2 (Rmax1/2) gradually fell with the degree of stenosis. The onset of significant mean flow reduction and ∆P was indicated by a drop of Rmax1/2 below 1 to 1.2. Thus, the analysis of high-resolution flow profiles allows detection of early hemodynamic changes even at degrees of stenoses not associated with a reduction of mean flow. Rmax1/2 allows differentiation of the grade of hemodynamic compromise for a given morphologic stenosis independent of mean flow in a single comprehensive MR examination.

Renal artery stenosis occurs in 0.01 to 45% of all patients, depending on the coexistence of various risk factors; in approximately 50% of the cases, the disease is progressive within a few years (1–4). It is a widely known cause of hypertension and renal insufficiency with the ultimate consequence of the need for dialysis. The diagnostic evaluation is challenging because multiple requirements have to be fulfilled. As the incidence of stenosis is highest in patients with coexisting atherosclerotic vascular disease or diabetes (1,2,5), these risk groups should be screened. Ideally, a screening technique should be accurate, reliable, noninvasive, and not dependent on the use of nephrotoxic contrast agents. Once a stenosis is confirmed, the hemodynamic and functional significance of the stenosis needs to be assessed. This is important in any workup for hypertension or renal insufficiency to decide whether the renal artery stenosis can be regarded as the main cause for the disease or more common causes such as essential hypertension or renal parenchymal disease have to be considered.

Magnetic resonance (MR) imaging has been established as a valuable tool for the assessment of renovascular disease because this technique combines the advantages of both morphologic and functional imaging. Contrast-enhanced three-dimensional gadolinium MR angiography (3D-Gd-MRA) is a noninvasive, safe technique that can detect and grade renal artery stenosis with high accuracy compared with digital subtraction angiography (6). Multiple functional MR methods allow evaluation of renal arterial flow, tissue perfusion, and filtration (7–9). The challenge for these techniques is to define parameters that can differentiate hemodynamically significant from nonsignificant stenoses. Because of autoregulation in the kidney, mean renal artery blood flow is preserved over a wide range of degrees of stenotic narrowing and therefore has limited diagnostic value with regard to the degree of stenosis.

Cardiac-gated MR cine phase-contrast flow measurements with high temporal resolution allow one to obtain time-resolved velocity profiles of the renal artery. Gradual hemodynamic changes secondary to a stenosis can be detected by means of characteristic changes of the velocity curve profile (10). The combination of these MR flow measurements and 3D-Gd-MRA allows for a comprehensive morphologic and functional evaluation of renovascular disease in a single examination (11).

The aim of this study was to define the correlation between the severity of renal artery stenosis and its hemodynamic significance. To this end, different morphologic degrees of
artificially created stenosis were systematically correlated to the corresponding changes in mean flow, pulsatile flow profile, and trans-stenotic pressure gradient in the renal artery in dogs to determine the respective hemodynamic significance. The objective was to define a parameter that reflects the degree of hemodynamic compromise for a given morphologic stenosis and renal blood flow change.

Materials and Methods

In chronically instrumented dogs, different morphologic degrees of renal artery stenosis were artificially created. For each degree of stenosis an ultra fast high resolution 3D gadolinium MR angiography was performed followed by cardiac-gated cine MR phase-contrast flow measurements with high temporal resolution. The results were correlated to invasive flow and pressure measurements.

Animals

All experiments were done on 11 chronically instrumented fox-hounds (weight, 24 to 31 kg). They had free access to water and were fed a standard dog diet (SSNIF, Soest, Germany). For invasive validation, MR-compatible transit-time flow probes (Transonic, Ithaca, NY) with a specially designed MR-compatible ceramic (Ma-cor, Fiberoptic, Spreitenbach, Switzerland) reflector were surgically implanted at the origin of the left renal artery approximately 2 mo before the measurements. An inflatable cuff was placed around the artery downstream to the flow probe. The surgical procedure has been described previously in more detail (12). The cuff was filled with saline with a small reservoir (5 ml) and controlled by pressurized air. In addition, a polyurethane catheter for recording arterial BP was implanted in the aorta (11 dogs) as well as in the renal artery (7 dogs) with its tip placed distally to the inflatable cuff. Catheters and cables were led subcutaneously to the dogs neck, where they were exteriorized. All experiments were done in accordance with the national guidelines for the care and use of research animals (license number 37-9185.81/156/96).

Invasive Measurements

The implanted flow probe was connected to an outside flowmeter (Transonic) to monitor mean and pulsatile renal blood flow after analog low-pass filtering (cutoff frequency, 100 Hz). Arterial pressure in the aorta and renal artery as well as trans-stenotic pressure gradients across the renal artery stenosis were determined with the catheters connected to pressure transducers (Statham P23XL) with calibrated amplifiers (Pressure processor, Gould, Cleveland, OH). All signals were converted into digital data (DAS-1602, Keithley METRABYTE, Taunton, MA) and recorded on a personal computer at a sampling rate of 200 Hz using the LabTech-Notebook (V7.11, Wilmington, MA) software. Different degrees of renal artery stenosis could be created by way of graded inflation of the implanted cuff.

MR Imaging Measurements

All measurements were performed on a clinical 1.5-T MR system (Magnetom Vision, Siemens Medical Systems, Inc., Iselin, NJ), equipped with a resonant echo planar imaging gradient overdrive (maximum gradient strength, 25 mT/m; shortest rise time to maximum, 300 µs). All examinations used the standard four-element phased-array body coil, centered at the level of the renal arteries. The animals were imaged in supine position. Cardiac gating was achieved with an optically decoupled ECG system (Siemens Medical Systems) placed on the shaved and depilated animals’ chest. The ECG signal was A/D converted and recorded synchronously with the invasive flow and pressure data. The animals’ aorta and renal arteries were localized with standard gradient echo sequences.

To obtain high-resolution Gd-enhanced MRA of good quality in the pure arterial phase, the acquisition had to be exactly synchronized with the arrival of the intravenously administered gadodiamide (Omniscan, Nycomed Amersham, Oslo, Norway) in the abdominal aorta. Therefore, the transit time of the Gd-chelate bolus was determined in the abdominal aorta with a test bolus sequence (repetition time [TR], 8.5 ms; echo time [TE], 4 ms; inversion recovery time, 100 ms) acquiring one image per s during infusion of 1 ml of gadodiamide at a rate 3 ml/s with a mechanical infusion system (Tomojet, Spectrospin, Bruker, Karlsruhe, Germany). Subsequently, the 3D-Gd-MRA was performed in the coronal plane during bolus administration of 20 ml of gadodiamide using a high-resolution 3D FLASH sequence with asymmetric k-space acquisition (11). With a minimum TR/TE of 4.5/1.5 ms, 80 partitions were reconstructed with an in-plane matrix of 205 × 512. For a field-of-view of 20 × 39 cm and a slab thickness of 6 cm, a spatial resolution of 1 × 0.7 × 0.7 mm was achieved. Based on the 3D-Gd-MRA data, cine phase-contrast flow measurements with prospective cardiac gating were performed in the renal artery as described previously (13). The scan plane was prescribed perpendicular to the vessel axis either 1 cm distal to the implanted inflatable cuff or immediately proximal to the flow probe. A 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 and resulted in a minimum temporal resolution of 2 × TR = 26 ms. For a full 256 × 256 matrix, a total measurement time of approximately 3 to 4 min was required. The in-plane spatial resolution equaled 0.9 × 0.9 mm (field of view, 22 cm) with a slice thickness of 6 mm.

The 3D-Gd-MRA data were reviewed in random order by two radiologists (readers 1 and 2). Each data set was individually evaluated using subvolume maximum intensity projections and multiplanar reformats. Both radiologists were blinded to each other’s rating as well as to the results of MR and ultrasound flow measurements. The morphologic degree of renal artery stenosis was classified angiographically according to the commonly used North American Symptomatic Carotid Endarterectomy Trial definition as follows:

% renal artery stenosis = (1 – [narrowest renal artery diameter/ diameter normal distal main renal artery]) × 100%

The phase-contrast data were analyzed off-line by a physicist on a workstation as described previously (10,13). The physicist was blinded to the results of the stenosis grading on 3D-Gd-MRA. 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.

Imaging Protocol

On the day of the experiment, the dog received pentobarbital sodium (Nembutal, SANOFI, Libourne, France; approximately 20 mg/kg intravenously) at least 1 h before the first measurement and 30 to 50 min after premedication with propionylpromazine (Combemal BAYER, Leverkusen, Germany; 0.5 mg/kg KG subcutaneously). If necessary, additional doses of pentobarbital were given (1 to 2 mg/kg per h). The dogs were breathing spontaneously during all experiments. Tracheal intubation was performed to allow the induction of apnea after manual hyperventilation. In all cases, the same protocol was performed as follows: After 30 s of manual hyperventilation, a high-
Cine phase-contrast flow measurements were performed in the left renal artery. Immediately before and after the phase-contrast flow measurements, invasive transit-time ultrasound flow measurements were obtained for a period of 2 to 4 min. Synchronous MR and ultrasound measurements were not possible because the radio frequency emitted during the MR image acquisition period interfered with the flowmeter. All measurements were repeated for four different degrees of stenosis induced by graded inflation of the implanted cuff. On the basis of previous results from stenotic arteries (10), the degree of stenosis was first estimated from the ultrasound flow curves by the characteristic changes in mean flow and pulsatile flow profile (see Results section). Five reproducible presets of cuff inflation were defined: (1) normal flow profile (no cuff inflation), (2) slight reduction of first (early) systolic peak, (3) stronger reduction of the early systolic peak but still larger than the second (midsystolic peak), (4) complete loss of the early systolic peak at the border of mean flow reduction, and (5) reduction of mean flow by 50% with decrease of the second (midsystolic) peak. The corresponding morphologic degree of renal artery stenosis \((1 - [\text{narrowest renal artery diameter/diameter normal distal main renal artery}]) \times 100%)\) was then retrospectively verified in the high-resolution 3D-Gd-MRA. The order of these different stenoses was randomly assigned.

In the three dogs with renal artery catheter and additional four dogs with the same instrumentation, transit-time ultrasound flow measurements were again recorded while the animals were conscious, resting in the laboratory (for more detail, see reference 12). Different degrees of stenosis were created by the same criteria as mentioned above. After a stabilization period of 3 min, data were recorded for 5 min. Subsequently, the stenosis was released and a 12-min recovery period was allowed before the next stenosis was induced. The order of the different stenoses was randomly assigned. Control recordings were done before the first and 12 min after the last stenosis. In four dogs, angiotensin II was continuously infused at the end of the experiment at a dose of 10 ng/kg per min to reduce mean flow by approximately 50%. Data were recorded for 5 min starting 10 min after the infusion.

Data Analysis

On the basis of the simultaneous ECG recordings, the MR and ultrasound flow curves were synchronized and identically scaled in milliliters per minute. The ultrasound flow profile was derived by signal averaging of the flow signal from all pulses detected by the ECG signal during the recording period using a custom-designed program.

In addition to mean flow, extracted from the time-resolved flow curves were three parameters that represent characteristic features of the renal artery flow profile: (1) first flow maximum (early systolic peak, \(\text{Max}_1\)) detected within the first 160 ms after the R-wave, (2) second flow maximum (midsystolic peak, \(\text{Max}_2\)) detected within 170 to 260 ms after the R-wave, (3) ratio of the first to the second flow maximum (\(\text{R}_{\text{max}1/2}\)). For standardization, \(\text{Max}_1\) and \(\text{Max}_2\) were expressed as percentage of mean flow (\(\text{Max}_1\%\), \(\text{Max}_2\%\)).

Comparison of MR and ultrasound flow measurements was carried out by means of a linear regression analysis and Bland-Altman plot (14). The numerical differences were assessed for statistical significance by means of a \(t\) test. All values were given as mean \(\pm\) SEM. On the basis of the high-resolution 3D-Gd-MRA findings, the MR and ultrasound flow data were correlated to the different degrees of renal artery stenosis. Statistical significance of differences in the values of arterial pressure (Table 1) was tested by Newman-Keuls test.

For the stenosis grading on 3D-Gd-MRA, interobserver agreement between readers 1 and 2 was assessed by a weighted \(k\) test. The \(k\) values were considered as slight for \(k \leq 0.2\), fair for \(k = 0.21 to 0.4\), moderate for \(k = 0.41 to 0.6\), substantial for \(k = 0.61 to 0.8\), and almost perfect for \(k = 0.81 to 1.00\) (15).

Table 1. Aortic pressure (AP), renal arterial pressure (RAP), and trans-stenotic pressure gradient (\(\Delta P\))

<table>
<thead>
<tr>
<th>Morphologic Degree of Stenosis (%)</th>
<th>0%</th>
<th>30%</th>
<th>50%</th>
<th>80%</th>
<th>&gt;90%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anesthetized with MR angiographic determination of degree of stenosis</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>AP (mmHg) ((n = 5))</td>
<td>105 \pm 5</td>
<td>119 \pm 6(^b)</td>
<td>117 \pm 5(^b)</td>
<td>120 \pm 4(^b)</td>
<td>128 \pm 7(^b)</td>
</tr>
<tr>
<td>RAP (mmHg) ((n = 3))</td>
<td>101 \pm 4</td>
<td>113 \pm 9 (^b)</td>
<td>109 \pm 7 (^b)</td>
<td>100 \pm 3 (^b)</td>
<td>50 \pm 6(^b)</td>
</tr>
<tr>
<td>(\Delta P) (mmHg) ((n = 3))</td>
<td>2 \pm 2</td>
<td>1 \pm 1 (^b)</td>
<td>3 \pm 1 (^b)</td>
<td>18 \pm 6(^c)</td>
<td>74 \pm 5(^c)</td>
</tr>
<tr>
<td><strong>Conscious without MR angiography (stenotic degree estimated from flow profile)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AP (mmHg) ((n = 7))</td>
<td>90 \pm 3</td>
<td>92 \pm 4 (^b)</td>
<td>92 \pm 4 (^b)</td>
<td>97 \pm 3 (^b)</td>
<td>102 \pm 2(^b)</td>
</tr>
<tr>
<td>RAP (mmHg) ((n = 7))</td>
<td>90 \pm 3</td>
<td>89 \pm 4 (^b)</td>
<td>81 \pm 2(^b)</td>
<td>68 \pm 4(^b)</td>
<td>40 \pm 3(^b)</td>
</tr>
<tr>
<td>(\Delta P) (mmHg) ((n = 7))</td>
<td>0 \pm 1</td>
<td>4 \pm 1 (^b)</td>
<td>11 \pm 2(^c)</td>
<td>28 \pm 4(^c)</td>
<td>62 \pm 3(^c)</td>
</tr>
</tbody>
</table>

\(^a\) MR, magnetic resonance.

\(^b\) \(P < 0.05\) versus 0%.

\(^c\) \(P < 0.05\) RAP versus AP.
In only one of the 35 reviewed renal arteries, there was disagreement between a high-grade (>90%) stenosis and a low-grade (≤80%) stenosis. In three cases, only minor disagreement between 0 and 30% degree of stenosis was found, in one case between 30 and 50% degree of stenosis. Therefore, all further final results were based on the data of reader 1.

MR demonstrated good agreement with the transit-time ultrasound recordings in the measurement of mean flow. This was true not only for the measurements in the normal renal artery but also for those performed during high-grade stenoses. The overall correlation coefficient was 0.78 (Figure 2A). No systematic deviation of the MR data from the ultrasound data was found. In the Bland-Altman plot, the largest differences between the MR and ultrasound data occurred for flow rates between 200 and 300 ml/min. The maximum deviation did not exceed 30% (Figure 2B).

The mean flow measurements obtained for 30%, 50%, and 80% stenosis did not significantly differ from those measured in the unstenosed vessel. A significant decrease in mean flow (P < 0.0001) of more than 50% was observed only for stenosis degrees greater than 90% (Figure 3A). No significant differences were found between the MR and ultrasound data. At the same time, no substantial trans-stenotic pressure gradients were identified for stenoses up to 50% and only mild gradients at a stenosis of 80%. In contrast, a stenosis greater 90% was associated with values of 70 mmHg and higher (Figure 3B, Table 1). This suggests that only stenoses of more than 90% are hemodynamically significant in terms of mean flow reduction. This flow reduction was due to a significant drop of the poststenotic pressure in the renal artery to values well below 60 mmHg, i.e., below the lower limit of renal blood flow autoregulation (Table 1). The activation of the renin angiotensin system and thus a possible relevance for renovascular hypertension is indicated by the increase of systemic arterial pressure (Table 1).

For the time-resolved flow curves, the following relationship could be identified between the morphologic degree of stenosis in the high-resolution MRA and the corresponding hemodynamic changes during the cardiac cycle (Figure 4): no stenosis, normal flow profile with presence of a large early systolic peak; 30% stenosis, slight decrease of early systolic peak; 50% stenosis, 50% loss of early systolic peak; 80% stenosis, complete loss of early systolic peak; >90% stenosis, decrease of mean flow.

As a result of these changes in the flow profile, the quantitative parameters Max1%, Max2%, and Rmax1/2 revealed substantially different values for the various degrees of stenosis (Table 2). Although Max1% was consistently higher than Max2% for 0%, 30%, and 50% stenosis, both reached approximately the same magnitude for the 80% degree of stenosis, thus representing the point at which Rmax1/2 had a value of approximately 1. For high-grade stenoses of more than 90%, the Rmax1/2 ratio declined to 0.75 as a result of the further loss of the early systolic peak (Figure 5). Significant changes both of mean flow and of trans-stenotic pressure gradients were associated almost exclusively with values of Rmax1/2 below a...
critical value of 1 to 1.2, whereas such changes were virtually absent for higher values of $R_{\text{max}}^{1/2}$.

A similar reduction of mean flow from angiotensin II administration resulted in fundamentally different effects on the flow profile than that observed with arterial stenosis. Whereas the flow curve was shifted to overall lower mean flow values after angiotensin II administration, no changes occurred in the general pattern of the flow profile with complete preservation of the early systolic peak (Figure 6). This is also reflected by $R_{\text{max}}^{1/2}$, which was $1.39 \pm 0.10$ during angiotensin II and $1.36 \pm 0.06$ under control conditions.

**Discussion**

In this study, three innovative steps are presented for a comprehensive noninvasive evaluation of renal artery stenosis. First, a systematic morphologic and functional evaluation of different degrees of renal artery stenosis is performed using noninvasive MR imaging. Second, characteristic hemodynamic changes are identified and correlated to the morphologic degree of stenosis. Third, derived are quantitative parameters that indicate whether pathologic changes of renal blood flow have occurred.

One cornerstone of the concept was the use of MR imaging. Because of the lack of nephrotoxicity of the contrast agent, repetitive measurements could be systematically performed in the same animal without inducing changes in renal function. Thereby, physiologic conditions were completely preserved. Since its introduction, contrast-enhanced 3D-Gd-MRA has been established as a reliable technique for grading renal artery stenosis; accuracy has been reported consistently to be greater than 90% (11). Usually, a spatial resolution of approximately 1.5 to 2 mm in each direction is sufficient for the human renal artery. In the canine renal artery, which has diameters of only approximately 5 mm, a higher spatial resolution is necessary. Therefore, a specially designed high-resolution technique with a voxel size below 1 mm$^3$ was applied; this allowed reliable grading of the degree of stenosis into at least five intervals with almost perfect interobserver agreement between two readers. The clinical high-performance MR scanner allowed use of short repetition and echo times. This resulted in two advantages. First, short scan times of only 30 s were feasible. After hyperventilation before the measurements, the MR angiograms thus could be obtained in apnea without breathing artifacts.
Second, the short echo times minimized artifacts from the implanted flow probes. In addition to the excellent visualization of morphology, noninvasive assessment of renal artery hemodynamics becomes immediately possible. The cardiac-gated MR phase-contrast flow measurements that were used are sufficient in terms of temporal and spatial resolution as well as accuracy to reveal identical findings as the invasive transit-time ultrasound flow measurements. This has, in part, been demonstrated in previous studies (13). The initially encouraging results could be confirmed in the present study with good correlation between the MR and ultrasound data. One important factor is the definition of the vessel area, which is critical for the accurate measurement of mean flow. In low-flow states, overestimation of the vessel area is usually highest as a result of the poor vessel signal-to-background ratio in the images. The error in mean flow calculation secondary to overestimation of the vessel area becomes worse at higher flow states. At the same time, however, the vessel area is better defined with higher blood flow signal in the vessel cross section. Therefore, the deviation was largest for intermediate flow values. It should be emphasized that the determination of the flow profile is less affected by the vessel area and thus is more robust.

For the first time, these two valid MR techniques are combined for a systematic comprehensive morphologic and functional evaluation of renal artery stenosis. As previously shown in both animal and human data (10,11,16), the pulsatile flow profile recorded in the renal artery during the cardiac cycle shows characteristic changes with varying degree of stenosis. Previously, it was impossible to define which hemodynamic changes correspond to the morphologic degree of stenosis. The combination of 3D-Gd-MRA and MR cine phase-contrast flow measurements address this by allowing repetitive measurements in the same animal. Up to a degree of stenosis of 80%, neither mean flow nor the trans-stenotic pressure gradient show significant changes. The only feature that indicates hemodynamic abnormalities in this range of stenosis is the gradual loss of the early systolic peak. The results were consistent throughout all seven animals. Agreement between MR and ultrasound data were excellent. The time-resolved MR curves were able to identify exactly the same changes as the implanted ultrasound flow probe. The only major difference, although clinically irrelevant, was the temporal offset between the ultrasound and MR flow curves of approximately 40 ms. This was caused by the lower temporal resolution of the MR technique of 26 ms as well as slight differences in the triggering of both measurements.

Identifying hemodynamic changes independent from changes in mean flow and pressure gradient has high clinical utility. Several considerations are appropriate in this context. First, renovascular disease is progressive. More than half of all stenoses progress to high-grade lesions within 3 yr (3,4). Because of the high autoregulatory capacity, mean renal artery blood flow will be maintained on a normal level until finally the autoregulatory capacity is exceeded and mean flow suddenly declines, leading to renal failure within a few years (17). Second, mean blood flow in patients is variable and depends on physiologic factors as well as on the presence of preexisting pathology, such as underlying renoparenchymal damage. Thus, an incidental measurement of mean flow might be inconclusive with respect to the question of whether an existing renal artery stenosis has already compromised renal artery blood flow. A significant renal artery stenosis has been identified as an independent predictor of intermediate-term patient survival (18). Third, the threshold pressure for pressure-dependent renin release is higher than the one for the lower limit of the autoregulatory capacity for blood flow (19,20). Thus, even low-grade stenoses that are too small to compromise mean flow may

Figure 4. Hemodynamic changes in the time-resolved flow profiles. The averaged data of seven dogs are presented. For reasons of clarity, error bars are given only for the normal flow curve (0% stenosis). With increasing degree of stenosis, the early systolic peak declines followed by a loss of the midsystolic maximum. Note the excellent agreement between the invasive transit-time ultrasound reference measurements (A) and the noninvasively obtained cardiac-gated MR flow measurements (B) with almost identical slope of the curves. Whereas the area under curve as a measure of mean flow does not substantially change up to 80% stenosis, the early systolic peak is sensitive to minor stenoses induced in the renal artery. The temporal offset between the ultrasound and MR flow curves of approximately 40 ms is caused by the lower temporal resolution of the MR technique as well as differences in the triggering of both measurements.
Activation of the renin-angiotensin system and thus may cause renovascular hypertension. The rise of systemic arterial pressure with increasing stenosis in the present study is consistent with this view. It should be noted, however, that the time periods during which the stenoses were present were too short for a complete development of renin-dependent hypertension (21). This might also explain the more severe hypertension in the anesthetized dogs, in which, for methodologic reasons, the duration of stenosis was longer than in the conscious dogs. Chronic reductions of renal arterial pressure may lead to much more severe hypertension than could be observed in this acute study because of additional intrarenal (22), systemic (23), and central nervous (24) effects. It is therefore necessary to identify a parameter of renal flow dynamics that is sensitive for both early hemodynamic changes and the lower limit of the autoregulatory capacity. In the present study, a minor decrease of the early systolic peak already indicated the presence of a low-grade stenosis up to 50%. For higher degrees of stenosis, the maximum of the early systolic peak fell below that of the midsystolic peak. This point indicated the onset of hemodynamic significance of the stenosis. This behavior was found to be very robust to interindividual variation and was consistently seen in all seven animals (Figures 4 and 5). Because anesthesia is known to impair renal autoregulation (25), the ultrasound measurements were repeated in conscious animals. As can be seen from Figure 5, in which the data from both anesthetized and conscious animals are given, this did not change the conclusions drawn from the results. Despite that in the MR measurement the early systolic peak was defined only by a few data points, the agreement with the real-time ultrasound data was substantial.

To demonstrate that the detected changes in the flow profile are specific for the presence of an arterial stenosis independent of the level of mean flow, the reduction of mean flow by means of mechanical stenosis was compared with similar reduction induced by angiotensin II infusion. Angiotensin II is known to substantially reduce mean flow while preserving the autoreg-

**Table 2.** Quantitative parameters derived from the changes in the renal artery flow profile in comparison to the morphologic degree of stenosis

<table>
<thead>
<tr>
<th>Morphologic Degree of Stenosis (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>0%</th>
<th>30%</th>
<th>50%</th>
<th>80%</th>
<th>&gt;90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$Max_1$ [%]</td>
<td>181 ± 21</td>
<td>175 ± 30</td>
<td>163 ± 36</td>
<td>164 ± 22</td>
<td>133 ± 18</td>
</tr>
<tr>
<td>$Max_2$ [%]</td>
<td>150 ± 24</td>
<td>153 ± 27</td>
<td>150 ± 30</td>
<td>158 ± 26</td>
<td>153 ± 30</td>
</tr>
<tr>
<td>$R_{max1/2}$</td>
<td>1.21 ± 0.06</td>
<td>1.15 ± 0.09</td>
<td>1.08 ± 0.07</td>
<td>0.99 ± 0.06</td>
<td>0.81 ± 0.10</td>
</tr>
<tr>
<td>MR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$Max_1$ [%]</td>
<td>189 ± 28</td>
<td>171 ± 24</td>
<td>168 ± 31</td>
<td>154 ± 26</td>
<td>131 ± 23</td>
</tr>
<tr>
<td>$Max_2$ [%]</td>
<td>143 ± 11</td>
<td>154 ± 14</td>
<td>147 ± 17</td>
<td>149 ± 18</td>
<td>177 ± 30</td>
</tr>
<tr>
<td>$R_{max1/2}$</td>
<td>1.34 ± 0.11</td>
<td>1.12 ± 0.06</td>
<td>1.14 ± 0.06</td>
<td>0.98 ± 0.06</td>
<td>0.76 ± 0.05</td>
</tr>
</tbody>
</table>

<sup>a</sup> Parameters are defined as first flow maximum (early systolic peak), second flow maximum (midsystolic peak) in percentage of mean flow ($Max_1$, $Max_2$), ratio of first to second flow maximum ($R_{max1/2}$).

<sup>b</sup> Morphologic degree of renal artery stenosis classified as % stenosis = ($\frac{\text{narrowest renal artery diameter}}{\text{diameter normal distal main renal artery}}$) × 100%.

**Figure 5.** Prediction of the hemodynamic significance of stenosis. The quantitative parameter of ratio of the first to second systolic maximum in percentage of mean flow ($R_{max1/2}$), which is extracted from the time-resolved flow profile (Figure 4), is correlated to mean flow (A) and the trans-stenotic pressure gradient (B). Pressure gradient is plotted as percentage of the baseline value. The data points represent the individual data for all five degrees of stenosis from all experiments in anesthetized (●, $n = 7$) and conscious (○, $n = 7$) dogs. A $R_{max1/2}$ value of 1.0 to 1.2 represents a numerical cutoff point below which significant changes in renal blood flow dynamics occur.
Figure 6. Comparison of hemodynamic changes evoked by arterial stenosis and angiotensin II. Mean ± SEM from four conscious dogs. An increasing degree of renal artery stenosis (∇) resulted in the typical changes of flow dynamics, with a progressive reduction of the first systolic peak ($R_{max1/2} = 0.83 \pm 0.07$ and $0.82 \pm 0.10$) and finally a depression of mean flow (MRBF). In contrast, infusion of angiotensin II (AngII, ●) did not affect the general pattern of the flow profile ($R_{max1/2} = 1.39 \pm 0.10$), despite a substantial reduction of mean flow as compared with the control condition ($R_{max1/2} = 1.36 \pm 0.06$).

ulatory capacity (26). Under these conditions, the shape of the flow curve was completely maintained with presence of a normal early systolic peak, while mean flow was even lower than in the stenotic artery. This was consistently seen in the four dogs studied.

In view of the potential clinical application, there was need to define from the flow curves quantitative parameters that predict the onset of mean flow reduction, i.e., the hemodynamic significance of stenosis. The introduced ratio of first and second maxima $R_{max1/2}$ is capable of assessing hemodynamic significance. A value of 1.0 to 1.2 indicated both the onset of a significant drop in mean flow and the increase of the trans-stenotic pressure gradient (Figure 5). This quantitative parameter can be introduced easily into the clinical MR evaluation of patients. A considerable number of patients have already been studied with the use of a combined morphologic and functional MR imaging protocol (11). Although similar hemodynamic changes were detected, these could not be systematically correlated to the morphologic degree of stenosis. The now introduced index $R_{max1/2}$, or “flow-pulse,” index can be used to define the hemodynamic significance of a detected stenosis in the presence of a normal or marginally low mean flow.

The abrupt change of mean flow and pressure gradient at a critical degree of stenosis emphasizes that the current morphologic-based grading of renovascular disease might not provide valuable parameters for the assessment of hemodynamic significance of renal artery stenosis. In contrast, the new parameters presented here are capable of identifying the onset of a hemodynamically significant stenosis at an early stage before mean flow is compromised.

Further evaluation of patient data is being done to transfer these parameters to chronic renal disease. In addition, needed is clarification of how significant changes in total renal flow translate into alterations in cortical versus medullary perfusion, as well as changes of excretory function. Changes of renal perfusion in the presence of acute or chronic renal artery stenosis already have been demonstrated using computer tomography (CT) or electron beam computed tomography (EBT) (27). In IR imaging, quantitative perfusion measurements with intravascular contrast agents, as well T1 measurements in the renal artery and vein during gadolinium infusion, are already available (9,28). In the future, these studies can be integrated in the existing protocol for a morphologic, hemodynamic, and functional evaluation within a single noninvasive examination.

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